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      Set  Items  Description
      ---  -----  -----------
? e au=hausdorff, w?

Ref   Items  Index-term
E1       30  AU=HAUSDORFF, W. P.
E2        2  AU=HAUSDORFF, W.P.
E3        0 *AU=HAUSDORFF, W?
E4        1  AU=HAUSDORFF, WENDELL JOHNSON
E5        1  AU=HAUSDORFF, WILLIAM
E6       19  AU=HAUSDORFF, WILLIAM P
E7       30  AU=HAUSDORFF, WILLIAM P.
E8        2  AU=HAUSDORFF, WILLIAM PAUL
E9       26  AU=HAUSDORFF, WP
E10       1  AU=HAUSDORFL, C.
E11       1  AU=HAUSDORIF JM
E12       2  AU=HAUSDORT G.

          Enter P or PAGE for more
? s e1-e8
              30  AU=HAUSDORFF, W. P.
               2  AU=HAUSDORFF, W.P.
               0  AU=HAUSDORFF, W?
               1  AU=HAUSDORFF, WENDELL JOHNSON
               1  AU=HAUSDORFF, WILLIAM
              19  AU=HAUSDORFF, WILLIAM P
              30  AU=HAUSDORFF, WILLIAM P.
               2  AU=HAUSDORFF, WILLIAM PAUL
      S1       85  E1-E8
? s s1 and (valent or serotype)
              85  S1
           58798  VALENT
          207443  SEROTYPE
      S2       20  S1 AND (VALENT OR SEROTYPE)
? rd

>>>Duplicate detection is not supported for File 393.

>>>Duplicate detection is not supported for File 391.

>>>Records from unsupported files will be retained in the RD set.
      S3       15  RD  (unique items)
? t s3/3,k/1-15
>>>KWIC option is not available in file(s): 399

 3/3,K/1     (Item 1 from file: 98)
DIALOG(R)File  98:General Sci Abs
(c) 2009 The HW Wilson Co. All rts. reserv.

04667992    H.W. WILSON RECORD NUMBER: BGSA01167992
Geographical differences for pneumococcal disease.
Pallares, Roman
Moreno, Georgina; Hausdorff, William P
Lancet (North American edition) (Lancet) v. 358 no9279 (Aug. 4 2001) p.
  419-20
SPECIAL FEATURES: bibl f   ISSN: 0099-5355
 LANGUAGE:  English
COUNTRY OF PUBLICATION: United States

Moreno, Georgina; Hausdorff, William P

...ABSTRACT:  clinical practice and patients' characteristics, the spread
```

of resistant clones might result in variations in serotype distribution and should be considered when planning vaccination strategies. A reply is published.

3/3,K/2 (Item 2 from file: 98)
DIALOG(R)File 98:General Sci Abs

04652943 H.W. WILSON RECORD NUMBER: BGSA01152943
Geographical differences in invasive pneumococcal disease rates and serotype frequency in young children.
Hausdorff, William P
Siber, George; Paradiso, Peter R
Lancet (North American edition) (Lancet) v. 357 no9260 (Mar. 24 2001) p. 950-2
SPECIAL FEATURES: bibl f graph ISSN: 0099-5355
LANGUAGE: English
COUNTRY OF PUBLICATION: United States

Geographical differences in invasive pneumococcal disease rates and serotype frequency in young children.
Hausdorff, William P

...ABSTRACT: the more than 90 pneumococcal serotypes are most likely to cause invasive pneumococcal disease (IPD). Serotype distribution is thought to vary geographically, even between regions as socioeconomically similar as western Europe...

...probably underdiagnosed and under-reported in western Europe. On the basis of a comparison of serotype distributions between the two regions, we also postulate that those serotypes found at similar frequencies...

3/3,K/3 (Item 1 from file: 162)
DIALOG(R)File 162:Global Health

0005407901 CAB Accession Number: 20083282163
Identification of pneumococcal serotypes from culture-negative clinical specimens by novel real-time PCR.
Tarrago, D.; Fenoll, A.; Sanchez-Tatay, D.; Arroyo, L. A.; Munoz-Almagro, C.; Esteva, C.; Hausdorff, W. P.; Casal, J.; Obando, I.
Author email address: davtarrago@isciii.es
Spanish Reference Laboratory for Pneumococci, Servicio de Bacteriologia, Centro Nacional de Microbiologia, Instituto de Salud Carlos III, Ctra. Majadahonda-Pozuelo km 2, 28220 Majadahonda, Madrid, Spain.
Clinical Microbiology and Infection vol. 14 (9): p.828-834
Publication Year: 2008
ISSN: 1198-743X
Digital Object Identifier: 10.1111/j.1469-0691.2008.02028.x
Publisher: Blackwell Publishing Oxford, UK
Language: English
Record Type: Abstract
Document Type: Journal article

... for the diagnosis of invasive pneumococcal disease and continued epidemiological surveillance in order to monitor serotype vaccine effectiveness.

Tarrago, D.; Fenoll, A.; Sanchez-Tatay, D.; Arroyo, L. A.; Munoz-Almagro, C.; Esteva, C.; Hausdorff, W. P.; Casal, J.; Obando, I.

3/3,K/4 (Item 2 from file: 162)
DIALOG(R)File 162:Global Health

0005391293 CAB Accession Number: 20083242947
Pediatric parapneumonic empyema, Spain.
Obando, I.; Munoz-Almagro, C.; Arroyo, L. A.; Tarrago, D.; Sanchez-Tatay, D.; Moreno-Perez, D.; Dhillon, S. S.; Esteva, C.; Hernandez-Bou, S.; Garcia-Garcia, J. J.; Hausdorff, W. P.; Brueggemann, A. B.
Author email address: iosantaella@telefonica.net
Virgen del Rocio Children's Hospital, Seville, Spain.
Emerging Infectious Diseases vol. 14 (9): p.1390-1397
Publication Year: 2008
ISSN: 1080-6040
Publisher: National Center for Infectious Diseases, Centers for Disease Control and Prevention Atlanta, USA
Language: English
Record Type: Abstract
Document Type: Journal article

... were genotyped by multilocus sequence typing. Serotypes were determined for 111 PPE cases; 48% were serotype 1, of 3 major genotypes previously circulating in Spain. Variance in patient complication rates was statistically significant by serotype. The recent PPE increase is principally due to nonvaccine serotypes, especially the highly invasive serotype 1.

...Moreno-Perez, D.; Dhillon, S. S.; Esteva, C.; Hernandez-Bou, S.; Garcia-Garcia, J. J.; Hausdorff, W. P.; Brueggemann, A. B.

3/3,K/5 (Item 3 from file: 162)
DIALOG(R)File 162:Global Health

0005372705 CAB Accession Number: 20083199798
Serotypes and pathogens in paediatric pneumonia.
Hausdorff, W. P.; Dagan, R.
Author email address: william.p.hausdorff@gsk.com\rdagan@bgu.ac.il
Epidemiology & Scientific Strategy, GlaxoSmithKline Biologicals s.a., Rue de l'Institut, 89, B-1330 Rixensart, Belgium.
Conference Title: Lessons from the past and implications for the future. First International Pneumonia Vaccines Workshop on Prevention of Childhood Pneumonia by Vaccination, Seoul, Korea Republic, 15 December 2007.
Vaccine vol. 26 (Supplement 2): p.B19-B23
Publication Year: 2008
ISSN: 0264-410X
Editors: Spier, R. E.
Publisher: Elsevier Amsterdam, Netherlands
Language: English
Record Type: Abstract
Document Type: Journal article; Conference paper

... specific pneumococcal serotypes and NTHi as pneumonia pathogens. While emerging conjugate vaccines, especially those containing serotype 1, appear to have great potential toward the prevention of childhood pneumonia based on expanded serotype coverage, the importance of NTHi in childhood pneumonia has yet to be elucidated.

Hausdorff, W. P.; Dagan, R.

3/3,K/6 (Item 4 from file: 162)
DIALOG(R)File 162:Global Health

0005337718 CAB Accession Number: 20083093822
Pneumococcal serotype epidemiology.
Hausdorff, W. P.; Brueggemann, A. B.; Hackell, J. G.; Scott, J. A. G.
GlaxoSmithKline Biologicals, Rue de l'Institut, 89, B-1330 Rixensart, Belgium.
Book Title: Pneumococcal vaccines: the impact of conjugate vaccine
p.139-160
Publication Year: 2008
Editors: Siber, G. R.; Klugman, K. P.; Makela, P. H.
Publisher: American Society for Microbiology (ASM) Washington, USA
ISBN: 978-1-55581-403-3
Language: English
Record Type: Abstract
Document Type: Book chapter

Pneumococcal serotype epidemiology.
Hausdorff, W. P.; Brueggemann, A. B.; Hackell, J. G.; Scott, J. A. G.

3/3,K/7 (Item 5 from file: 162)
DIALOG(R)File 162:Global Health

0005049609 CAB Accession Number: 20053019887
Epidemiological differences among pneumococcal serotypes.
Hausdorff, W. P.; Feikin, D. R.; Klugman, K. P.
Author email address: william.p.hausdorff@gsk.com
GlaxoSmithKline Biologicals, 2301 Renaissance Blvd, RN0220, PO Box 61540, King of Prussia, PA 19406-2772, USA.
Lancet Infectious Diseases vol. 5 (2): p.83-93
Publication Year: 2005
ISSN: 1473-3099
Digital Object Identifier: 10.1016/S1473-3099(05)01280-6
Publisher: Elsevier Oxford, UK
Language: English
Record Type: Abstract
Document Type: Journal article

... vaccines are directed at specific serotypes, national immunisation advisory committees may wish to consider these serotype-specific properties when considering which vaccine formulation to introduce into a national programme.

Hausdorff, W. P.; Feikin, D. R.; Klugman, K. P.

3/3,K/8 (Item 6 from file: 162)
DIALOG(R)File 162:Global Health

0004901836 CAB Accession Number: 20023187496
Multinational study of pneumococcal serotypes causing acute otitis media in children.
Hausdorff, W. P.; Yothers, G.; Dagan, R.; Kilpi, T.; Pelton, S. I.; Cohen, R.; Jacobs, M. R.; Kaplan, S. L.; Levy, C.; Lopez, E. L.; Mason, E.

O., Jr.; Syriopoulou, V.; Wynne, B.; Bryant, J.
Author email address: Hausdowp@wyeth.com
Wyeth Vaccines, 211 Bailey Road, West Henrietta, NY 14586, USA.
Pediatric Infectious Disease Journal vol. 21 (11): p.1008-1016
Publication Year: 2002
ISSN: 0891-3668
Digital Object Identifier: 10.1097/00006454-200211000-00007
Publisher: Lippincott Williams & Wilkins Hagerstown, USA
Language: English
Record Type: Abstract
Document Type: Journal article

...comprised 5 to 10%. Despite differences in location, study design and antibiotic susceptibility, each major serotype was prominent in most age groups of each dataset. Serotypes represented in the 7-valent pneumococcal conjugate vaccine (PCV-7, 4, 6B, 9V, 14, 18C, 19F, 23F) accounted for 60...

...range, but only 40 to 50% of isolates in children <6 or >=60 months old. Serotype 3 and, in certain datasets, serotypes 1 and 5, were more important in the <6...

Hausdorff, W. P.; Yothers, G.; Dagan, R.; Kilpi, T.; Pelton, S. I.; Cohen, R.; Jacobs, M...

3/3,K/9 (Item 7 from file: 162)
DIALOG(R)File 162:Global Health

0004838405 CAB Accession Number: 20013171047
Pneumococcal conjugate vaccine serotypes of Streptococcus pneumoniae isolates and the antimicrobial susceptibility of such isolates in children with otitis media.
Joloba, M. L.; Windau, A.; Bajaksouzian, S.; Appelbaum, P. C.; Hausdorff, W. P.; Jacobs, M. R.
Department of Pathology, Case Western Reserve University, University Hospitals of Cleveland, 11100 Euclid Ave., Cleveland, OH 44106, USA.
Clinical Infectious Diseases vol. 33 (9): p.1489-1494
Publication Year: 2001
ISSN: 1058-4838
Digital Object Identifier: 10.1086/323027
Publisher: University of Chicago Press Chicago, USA
Language: English
Record Type: Abstract
Document Type: Journal article

The ability of the recently licensed 7-valent pneumococcal conjugate vaccine to cover isolates that cause otitis media, especially drug-resistant ones, was...
... 84%) belonged to vaccine-related serogroups, whereas 82 (16%) belonged to non-vaccine-related serogroups. Serotype 3 accounted for 48 (59%) of the non-vaccine-related serogroups. In addition, 93% of...

... vaccine, including 95.1% of the isolates from patients <2 years of age. The 7-valent pneumococcal conjugate vaccine could therefore potentially provide protection against all but 1 (type 3) of...

Joloba, M. L.; Windau, A.; Bajaksouzian, S.; Appelbaum, P. C.; Hausdorff, W. P.; Jacobs, M. R.

3/3,K/10 (Item 8 from file: 162)

0004760741 CAB Accession Number: 20002009737
The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, part II.
Hausdorff, W. P.; Bryant, J.; Kloek, C.; Paradiso, P. R.; Siber, G. R.
Wyeth-Lederle Vaccines, 211 Bailey Road, West Henrietta, NY 14586, USA.
Clinical Infectious Diseases vol. 30 (1): p.122-140
Publication Year: 2000
ISSN: 1058-4838
Digital Object Identifier: 10.1086/313609
Language: English
Record Type: Abstract
Document Type: Journal article

... slightly less frequently from CSF than from blood or MEF. Nonetheless, serogroups in the 9-valent conjugate vaccine formulation still comprised ~75% of pneumococcal isolates from the CSF of young children...

Hausdorff, W. P.; Bryant, J.; Kloek, C.; Paradiso, P. R.; Siber, G. R.

3/3,K/11 (Item 9 from file: 162)

0004759495 CAB Accession Number: 20002009318
Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I.
Hausdorff, W. P.; Bryant, J.; Paradiso, P. R.; Siber, G. R.
Wyeth-Lederle Vaccines, 211 Bailey Road, West Henrietta, NY 14586, USA.
Clinical Infectious Diseases vol. 30 (1): p.100-121
Publication Year: 2000
ISSN: 1058-4838
Digital Object Identifier: 10.1086/313608
Language: English
Record Type: Abstract
Document Type: Journal article

... young children and older children/adults, respectively, in each geographic region. Serogroups in the 7-valent formulation (4, 6, 9, 14, 18, 19, and 23) cause 70%-88% of IPD in...

... Oceania, Africa, and Europe, and <65% in Latin America and Asia. Serogroups in the 9-valent formulation (7-valent + 1, 5) cause 80%-90% of IPD in each region except Asia (66%). Serogroup 1...
...and Canada and Oceania. In contrast, several serogroups not found in 7-, 9-, and 11-valent conjugate formulations are significant causes of disease in older children/adults. Nevertheless, each conjugate formulation ...

Hausdorff, W. P.; Bryant, J.; Paradiso, P. R.; Siber, G. R.

3/3,K/12 (Item 1 from file: 399)

149582415 CA: 149(26)582415p PATENT

Multivalent pneumococcal polysaccharide-protein conjugate composition
INVENTOR(AUTHOR): Hausdorff, William P.; Siber, George Rainer; Paradiso, Peter R.; Prasad, A. Krishna
LOCATION: USA
ASSIGNEE: Wyeth, John, and Brother Ltd.
PATENT: PCT International ; WO 2008143709 A2 DATE: 20081127
APPLICATION: WO 2007US86941 (20071210) *US 2006644924 (20061222)
PAGES: 59pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
IPCR/8 + Level Value Position Status Version Action Source Office:
A61K-0039/00 A I F B 20060101 H EP
A61P-0035/00 A I L B 20060101 H EP
DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BH; BR; BW; BY; BZ; CA; CH; CN; CO; CR; CU; CZ; DE; DK; DM; DO; DZ; EC; EE; EG; ES; FI; GB; GD; GE; GH; GM; GT; HN; HR; HU; ID; IL; IN; IS; JP; KE; KG; KM; KN; KP; KR; KZ; LA; LC; LK; LR; LS; LT; LU; LY; MA; MD; ME; MG; MK; MN; MW; MX; MY; MZ; NA; NG; NI; NO; NZ; OM; PG; PH; PL; PT; RO; RS; RU; SC; SD; SE; SG; SK; SL; SM; SV; SY; TJ; TM; TN; TR; TT; TZ DESIGNATED REGIONAL: AT; BE; BG; CH ; CY; CZ; DE; DK; EE; ES; FI; FR; GB; GR; HU; IE; IS; IT; LT; LU; LV; MC; MT; NL; PL; PT; RO; SE; SI; SK; TR; BF; BJ; CF; CG; CI; CM; GA; GN; GQ; GW; ML; MR; NE; SN; TD; TG; BW; GH; GM; KE; LS; MW; MZ; NA; SD; SL; SZ; TZ; UG; ZM; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM

3/3,K/13 (Item 1 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

03823739 SUPPLIER NUMBER: 185210251 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Pediatric parapneumonic empyema, Spain.(RESEARCH)
Obando, Ignacio; Munoz-Almagro, Carmen; Arroyo, Luis A.; Tarrago, David; Sanchez-Tatay, David; Moreno-Perez, David; Dhillon, Sahar S.; Esteva, Cristina; Hernandez-Bou, Susanna; Garcia-Garcia, Juan J.; Hausdorff, William P.; Brueggemann, Angela B.
Emerging Infectious Diseases, 14, 9, 1390(8)
Sept,
2008
PUBLICATION FORMAT: Magazine/Journal ISSN: 1080-6040 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Academic; Professional
WORD COUNT: 5124 LINE COUNT: 00569

...Hausdorff, William P

TEXT:
...were genotyped by multilocus sequence typing. Serotypes were determined for 111 PPE cases; 48% were serotype 1, of 3 major genotypes previously circulating in Spain. Variance in patient complication rates was statistically significant by serotype. The recent PPE increase is principally due to nonvaccine serotypes, especially the highly invasive serotype 1.
... genotypes recovered from northern and southern Spain in the context of regional differences in 7-valent pneumococcal conjugate vaccine (PCV7) uptake; and 4) identify any differences between highly invasive serotypes and...

...isolated from 53 (79%) of these cases (Figure 2). In 51 of these, a pneumococcal serotype could be identified via the conventional Quellung reaction. Evidence of pneumococcal infection in 99 (84...

...positive/wzg-positive and 2 ply-negative/wzg-positive) had a sufficient sample to enable serotype testing by PCR. In 52 of these samples, a serotype could be identified. Thus, a pneumococcal serotype was

identified in 103 PF samples (Figure 2).

In addition, a predicted serotype based on MLST genotyping was established for 2 cases with negative PCR results and 6...

...was possible (Figure 2). Such predictions were possible because there is a strong relationship between serotype and MLST genotype for most genotypes (16-18; www.mlst.net), with the exception of a small number of well-known genotypes that are associated with different serotype variations.

Eighty-one PF samples were fully genotyped, and 18 were partially genotyped ((greater than...

...predicted serotypes (Figure 2). Eighteen PF samples were partially genotyped by MLST: 2 were presumptive serotype 1 pneumococci based on 5-6 loci matching ST228; 1 was a presumptive serotype 5 based on 5 loci matching ST1223; 7 were genotyped at (greater than or equal to) 4 loci and serotyped by PCR (serotype 1, n = 5; serotype 7F and 19A, n = 1 each); and 8 samples were partially genotyped at (greater than...

...serotypes based on incomplete genotyping data were not included in further analyses.

(FIGURE 1 OMITTED)

Serotype Distribution

Ten serotypes were identified among the 111 PPE cases with tentatively assigned or confirmed serotyping information (Table 2). Non-PCV7 serotypes caused 96 (89%) cases of PPE, including serotype 1, which was detected in 48% of the patient samples. Although a significantly higher proportion...

...005), but there were no significant regional differences in vaccination status among children infected with serotype 1 (28% vs. 22%, p = 0.63).

(FIGURE 2 OMITTED)

Eight (15%) of 53 cultured pneumococci were intermediately penicillin resistant and 4 (8%) were resistant at high levels. Serotype 1, 3, 5, and 7F pneumococci were uniformly susceptible to penicillin and significantly more common...

...PF samples were fully genotyped; 26 STs were identified (Table 3). Three of the major serotype 1 STs (18), ST228, ST304 and ST306, were identified, although ST228 was only detected in...

...related single-locus variant, ST1223; and ST191 ((Netherlands.sup.7F)-39), respectively.

Six of 7 serotype 14-positive PF samples were ST156 ((Spain.sup.9V)-3). Genotypic diversity among the serotypes in this study was greatest for serotype 19A; 5 unrelated STs were detected, including ST81 ((Spain.sup.23F)-1). Such variants of...

...isolates were also genotyped. Twenty-three percent (29/126) of all IPD was due to serotype 1. Over this period, there was a statistically nonsignificant increase in the proportion of IPD cases due to serotype 1:17% (2001-2003) vs. 27% (2004-2006), p = 0.19.

Twenty-four serotypes were...

...6B, 11, 13, 15A, 16, 18C, 22, 23A, 23B, 23F, 24, 33, 34, and 38). Serotype 1 isolates were almost exclusively associated with pulmonary disease, including bacteremic pneumonia (12/29, 41%) and PPE (15/29, 52%). The 3 major serotype 1 PPE genotypes were also found among this collection of serotype 1 IPD isolates, although ST304 was no longer detected after 2002 and ST306 was first detected in 2003. A retrospective analysis of serotype 1 invasive isolates submitted to the Spanish National Reference Laboratory since 1990 showed ongoing circulation of

ST228 and ST304, but ST306 was only detected once before 2000 (1998; unpub, data).

Serotype 14 was the second most common IPD-causing serotype, with an overall prevalence of 17% (23% in 2001-2003 and 12% in 2004-2006; p = 0.12). The major serotype 14 genotype (ST156) identified in PF samples was also detected throughout the entire 2001-2006 ...

...causing pulmonary disease (Table 4). Ten (8%) cases of culture-positive IPD were due to serotype 7F, 9 of which were detected after 2004. ST191 was the only serotype 7F genotype in IPD and NP carriage.

Serotype-Specific Differences in Clinical Epidemiology, Inflammatory Markers, and Outcome

PPE-associated serotypes were divided into...

...groups: 1) serotypes 1, 5, 7F, and 14, consistently associated with the highest estimates of serotype-specific high invasive disease potential (HIDP) (16,17,19); 2) serotype 3 alone; and 3) serotypes 6A, 9V, 19A, and 23F, which have a low invasive...

...1 (n = 53) and 5 (n = 9) and comprised children >36 months of age, whereas serotype 14 (n = 9) only caused PPE in patients <36 months of age (data not shown; p = 0.0001). Serotype 3 PPE was associated with significantly more complications than PPE caused by HIDP and LIDP...

...the culture-positive and culture-negative cases of PPE, which was mainly associated with nonvaccine serotype 1 followed by 3, 5, 7F, and 19A, as well as vaccine serotype 14. Serotypes 1, 3, and 14 in particular are well-known PPE-associated serotypes (2...

...in PPE surveillance when surveillance is based solely on conventional microbiologic culture methods. Infection with serotype 3 was a risk factor independently associated with PPE complications, a finding also seen in a US study (22).

Serotype 1 has also been the most prevalent IPD serotype among Spanish children <14 years of age, representing 5%, 11%, and 27% of all culture...

...the Pneumococcal Reference Laboratory in 1997, 2003, and 2006, respectively (23). However, the increase in serotype 1 disease cannot easily be explained by a vaccine effect, in part because PCV7 coverage...

...34%-45% in 2004-2005 (24,25).

In addition, increased PPE incidence largely caused by serotype 1 was reported in the United States and the United Kingdom in the decades before...

...4,6,20). Previous studies have suggested that the high year-to-year variability of serotype 1 and 5 disease may represent large-scale outbreaks of a cyclical nature (26-28).

However, the observation in this study that 2 of the 3 MLST genotypes of serotype 1 (ST228 and ST304) had been "resident" in Spain at least since 1990 indicates that serotype 1 PPE increases in Spain were likely not due to a recent introduction of a...
...not enable a longer-term analysis of PPE epidemiology. Second, our analyses relied exclusively on serotype identification and MLST genotyping, neither of which detects differences in virulence factors apart from the serotype. Genetic factors independent of the capsule have been associated with invasiveness and disease severity (17...

...to less severe pneumonia cases, whose etiology may be qualitatively different.

Unfortunately, PCV7 has a serotype coverage of only 11%-14%

(including the cross-reactive 6A) in the population of PPE...

...However, conjugate vaccines containing serotypes 1, 5, and 7F, such as the newly developed 10-valent pneumococcal Haemophilus influenzae protein D conjugate vaccine candidate (35), could increase the serotype coverage for PPE up to 80%; the subsequent addition of serotypes 3 and 19A in...

...E, Peto T, Crook DW, Spratt BG. Clonal relationships between invasive carriage Streptococcus pneumoniae and serotype- and clone-specific differences in invasive disease potential. J Infect Dis. 2003;187:1424-32
...
...Olsson-Liljequist B, Christensson B, Samuelsson A, Kronvall G, et al. Effect of clonal and serotype-specific properties on the invasive capacity of Streptococcus pneumoniae. J Infect Dis. 2004;189:785...

...1086/381686
(18.) Brueggemann AB, Spratt BG. Geographic distribution and clonal diversity of Streptococcus pneumoniae serotype 1 isolates. J Clin Microbiol. 2003;41:4966-70. DOI: 10.1128/JCM.41.11...

...Setas A, Torroba L, Navarro-Alonso JA, Irisarri F, et al. Effectiveness of the 7-valent pneumococcal conjugate vaccine: a population-based case-control study. Clin Infect Dis. 2007;44:1436...

...Belmaker I, Porat N, Siton Y, Weber G, et al. An outbreak of Streptococcus pneumoniae serotype 1 in a closed community in southern Israel. Clin Infect Dis. 2000;30:319-21...

...Dis. 2003;35:452-8. DOI: 10.1080/00365540310013315
(31.) UK Health Protection Agency. Pneumococcal serotype distribution for samples referred for serotyping epidemiological years (July-June): 2000/1a005/6 (cited 2007...
...Hinds J, Smith A, Clarke SC, et al. Genomic diversity between strains of the same serotype and multilocus sequence type among pneumococcal clinical isolates. Infect Immun. 2006;74:3513-8. DOI...

...5. DOI: 10.1086/498897
(35.) Hausdorff WP, Brneggemann AB, Hackell J, Scott JAG. Pneumococcal serotype epidemiology. In: Siber GR, Klugman KP, Makela PH, editors. Pneumococcal vaccines: the impact of conjugate...

...than or equal to)1 dose, % 31
Referral, % 38

* PPE, pediatric parapneumonic empyema; PCV7, 7-valent pneumococcal
conjugate vaccine.
...2
d (range 1-10 d).

Table 2 Pneumococcal serotypes identified among pleural fluid samples

Serotype *	Barcelona, no. (%), n = 56	Seville/Malaya, no. n = 55
1	27 (48)	26 (47)
7F...		
...2 (4)	0	
6A	2 (4)	0
8	0	1 (2)
19F	1 (2)	0

Serotype *	Total, no. (%), n = 111	p value
1	53 (48)	0.92
7F	14 (13)	0...

...2 (2) 0.50
8 1 (0.9) 1
19F 1 (0.90 1

* 7-valent
pneumococcal conjugate vaccine serotypes include 4, 6B, 9V,
14, 18C, 19F, 23F. Pleural fluid samples...
...6 years of aye, Seville * ((dagger))

Serotype	NO. (%) patients with IPD, n = 126	STs detected: diseases detected (no. patients), n = 111
1	29 (32)	228: P (7), PPE (6), A (1...

...53: M (1)

Serotype	Carriage, no. (%) patients, n = 194	STs detected in carriage (no. patients)	OR (95% CI)
1	1 (1)	306 (1)	57.7 (7.7-429.9)
14	15...		

...the study period in
Seville, Malaga, and Barcelona. An OR demonstrating the potential
for each serotype to cause invasive disease, relative to its
prevalence in nasopharyngeal carriage, was also calculated (16...

...2003.

((section)) First detected in 2002.

Table 5. Characteristics of children hospitalized with PPE, by
serotype category, excluding patients with serious underlying
disease (n=3) *

Characteristic	HIDP serotyhes, n = 84	Serotype 3, n = 11
Median age, mo (range)	55.6 (2-180)	37.9...

...significant differences between individual groups by
post hoc analysis (p = 0.023 for comparison between serotype
3 and
LIDP)

((paragraph)) Complications included (no. patients): bronchopleural
fistula (3), pyopneumothorax (2), pneumatoceles (4...

...48 h (2), severe anemia requiring
blood transfusion (2), severe hypoalbuminemia requiring seroalbumin

replacement (1).

Serotype 3 compared withHIDP and LIDP groups combined.

3/3,K/14 (Item 2 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

02011727 SUPPLIER NUMBER: 77032076 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Geographical differences for pneumococcal disease.(Brief Article)(Letter to the Editor)
Paradiso, Peter R; Siber, George; Hausdorff, William P; Linares, Josefina; Tubau, Fe; Moreno, Georgina; Pallares, Roman
The Lancet, 358, 9279, 419
August 4,
2001
DOCUMENT TYPE: Brief Article; Letter to the Editor PUBLICATION FORMAT: Magazine/Journal; Refereed ISSN: 0099-5355 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 1318 LINE COUNT: 00111

...Hausdorff, William P
... countries such as the UK, Germany, Denmark, and Finland.(2)
The spread of a resistant serotype can occur among young children (eg, in day-care centres)(3) and adults (eg, in...

...are probably similar, or even worse, than those made in the other western European countries.
Serotype distribution may vary over time. Thus, in our hospital for adult patients, from 1979 to...

...in clinical practice and patients' characteristics, the spread of resistant clones may produce variations in serotype distribution, and should be taken into account in planning vaccination strategies.
(*) Roman Pallares, Georgina Moreno...

...es)
(1) Hausdorff WP, Siber G, Paradiso PR. Geographical differences in invasive pneumococcal disease and serotype frequency in young children. Lancet 2001; 357: 950-52.
(2) Sankilampi U, Herva E, Haikula...

...of antibiotic resistance in a given population could potentially have an important impact on the serotype distribution.
However, we do not agree with their assertion that the distribution of serotypes causing...

...study, around 74% of IPD-causing serogroups in Spanish children were represented in the 7-valent conjugate vaccine formulation (4, 6, 9, 14, 19, 23), and serotypes 1 and 5 accounted...
...in line with most studies from western Europe, and contrast with the 85-90% 7-valent serogroup coverage range consistently reported for US and Canadian studies, with serotypes 1 and 5...

...suggest that this factor is crucial for determining serogroup distribution in that country. However, 7-valent serogroup coverage for IPD in Spanish children younger than 5 years (78%)(1) is similar...

...but only 63% in those aged 2-5 years, were serogroups represented in the 7-valent formulation. Similar striking differences between those

3/3,K/15 (Item 3 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

01979670 SUPPLIER NUMBER: 72341085 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Geographical differences in invasive pneumococcal disease rates and serotype frequency in young children.(Hypothesis)
Hausdorff, William P; Siber, George; Paradiso, Peter R
The Lancet, 357, 9260, 950
March 24,
2001
PUBLICATION FORMAT: Magazine/Journal; Refereed ISSN: 0099-5355
LANGUAGE: English RECORD TYPE: Fulltext; Abstract TARGET AUDIENCE: Professional
WORD COUNT: 2671 LINE COUNT: 00223

Geographical differences in invasive pneumococcal disease rates and serotype frequency in young children.(Hypothesis)
Hausdorff, William P...

TEXT:

...the more than 90 pneumococcal serotypes are most likely to cause invasive pneumococcal disease (IPD). Serotype distribution is thought to vary geographically, even between regions as socioeconomically similar as western Europe...

...probably underdiagnosed and under-reported in western Europe. On the basis of a comparison of serotype distributions between the two regions, we also postulate that those serotypes found at similar frequencies...
... this variation is the difference between western Europe and North America; a recently licensed 7-valent conjugate vaccine reportedly covers 68-81% of serogroups in young children in western Europe, and...

...that a considerable proportion of mild IPD is normally unrecognised.(15)

Regional differences in IPD serotype distribution are skewed by differences in the patient populations sampled. If some serotypes or serogroups...

...have ratios near to 1, suggesting that they mainly cause severe IPD. Thus, even though serotype 1 causes 5% of IPD in western Europe and only 0.5% in the USA, the rates of serotype 1 disease in these regions are each about 0.9 per 100000 children/year. The...are rare.

To what extent might differences in local blood-culture practices affect interpretation of serotype results in other contexts? In some regions the willingness to take a blood sample depends on the age of the child, which complicates cross-study comparisons of serotype distribution in paediatric populations with different age distributions. From a historical perspective, interpretation of changes in serotype distribution since the 1930s in the USA needs to take into account increases in the...
...include in a vaccine.

Hypothesis

We suggest that a large proportion of geographical variation in serotype distribution is attributable to differences in selection of patients and blood-culture practices. However, some true regional variations in serotype prevalence--eg, serotype 21--probably exist, especially outside the USA and Europe.

Testing the hypothesis

Direct testing of our hypothesis would require a prospective investigation of serotype monitoring and IPD rates in several countries, in which precise ages, disease manifestations, and blood...

...world could substantially affect the perceived coverage of multivalent pneumococcal-conjugate vaccines. The new 7-valent vaccine might prevent a greater proportion of overall IPD burden in European and Latin American...

...they are prescribed antibiotics before diagnosis. Conversely, if certain serotypes not contained in the 7-valent vaccine are disproportionately responsible for severe disease, this vaccine might prevent a slightly smaller proportion...1998; 30: 257-62.
(20) Butler JC, Breiman RF, Lipman HB, Hofmann J, Facklam RR. Serotype distribution of Streptococcus pneumoniae infections among preschool children in the United States, 1978-1994: implications...

...Drug Resist 1997; 3: 111-15.
(27) Scott JAG, Hall AJ, Hannington A, et al. Serotype distribution and prevalence of resistance to benzylpenicillin in three representative populations of Streptococcus pneumoniae isolates...
? e au=siber, george?

```
Ref   Items  Index-term
E1        2  AU=SIBER, GEORGE R. SIBER
E2        8  AU=SIBER, GEORGE RAINER
E3        0 *AU=SIBER, GEORGE?
E4        1  AU=SIBER, GERLINDE
E5      151  AU=SIBER, GR
E6        4  AU=SIBER, GR*
E7        1  AU=SIBER, H.
E8        3  AU=SIBER, H.J.
E9        4  AU=SIBER, HANS
E10       1  AU=SIBER, HANS-JAKOB
E11       2  AU=SIBER, HARALD
E12       5  AU=SIBER, I.

          Enter P or PAGE for more
? s e1-e6
                2  AU=SIBER, GEORGE R. SIBER
                8  AU=SIBER, GEORGE RAINER
                0  AU=SIBER, GEORGE?
                1  AU=SIBER, GERLINDE
              151  AU=SIBER, GR
                4  AU=SIBER, GR*
      S4      166  E1-E6
? s s4 and (valent or serotype)
              166  S4
            58798  VALENT
           207443  SEROTYPE
      S5       18  S4 AND (VALENT OR SEROTYPE)
? rd

>>>Duplicate detection is not supported for File 393.

>>>Duplicate detection is not supported for File 391.

>>>Records from unsupported files will be retained in the RD set.
      S6        9  RD  (unique items)
? t s6/3,k/1-9
>>>KWIC option is not available in file(s): 399

 6/3,K/1     (Item 1 from file: 24)
DIALOG(R)File  24:CSA Life Sciences Abstracts
(c) 2009 CSA. All rts. reserv.

0003317997       IP ACCESSION NO: 8372669
```

Comparison of Pneumococcal Conjugate Polysaccharide and Free Polysaccharide Vaccines In Elderly Adults: Conjugate Vaccine Elicits Improved Antibacterial Immune Responses and Immunological Memory

de Roux, A; Schmoeele-Thoma, B; Siber, GR; Hackell, JG; Kuhnke, A ; Ahiers, N; Baker, SA; Razmpour, A; Emini, EA; Fernsten, PD; Gruber, WC; Lockhart, S; Burkhardt, O; Weite, T; Lode, HM
Center for Respiratory Medicine at the Charlottenburg Castle, Pneumologische Praxis am Schloss Chariottenburg, Spandauer Damm 3, 14059 Berlin, Germany, [mailto:aderoux@aol.com]

Clinical Infectious Diseases, v 46, n 7, p 1015-1023, April 1, 2008
PUBLICATION DATE: 2008

DOCUMENT TYPE: Journal Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English
ISSN: 1058-4838
FILE SEGMENT: Industrial & Applied Microbiology Abstracts (Microbiology A); Immunology Abstracts

de Roux, A; Schmoeele-Thoma, B; Siber, GR; Hackell, JG; Kuhnke, A ; Ahiers, N; Baker, SA; Razmpour, A; Emini, EA; Fernsten, PD...

ABSTRACT:
... in a comprehensive adult immunization strategy. Methods. We compared the immunogenicity and safety of 7-valent PnC vaccine (7vPnC) with that of 23-valent pneumococcal polysaccharide vaccine (PPV) in adults greater than or equal to 70 years of age...

6/3,K/2 (Item 2 from file: 24)
DIALOG(R)File 24:CSA Life Sciences Abstracts

0002743752 IP ACCESSION NO: 6421900
Serum Serotype-Specific Pneumococcal Anticapsular Immunoglobulin G Concentrations after Immunization with a 9-Valent Conjugate Pneumococcal Vaccine Correlate with Nasopharyngeal Acquisition of Pneumococcus

Dagan, R; Givon-Lavi, N; Fraser, D; Lipsitch, M; Siber, GR; Kohberger, R
Pediatric Infectious Disease Unit, Soroka University Medical of Health Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Journal of Infectious Diseases, v 192, n 3, p 367-376, August 1, 2005
PUBLICATION DATE: 2005

DOCUMENT TYPE: Journal Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English
ISSN: 0022-1899
FILE SEGMENT: Bacteriology Abstracts (Microbiology B); Immunology Abstracts
Serum Serotype-Specific Pneumococcal Anticapsular Immunoglobulin G Concentrations after Immunization with a 9-Valent Conjugate Pneumococcal Vaccine Correlate with Nasopharyngeal Acquisition of Pneumococcus

Dagan, R; Givon-Lavi, N; Fraser, D; Lipsitch, M; Siber, GR;

Kohberger, R

ABSTRACT:
... conjugate vaccines (PCVs) reduces nasopharyngeal colonization by Streptococcus pneumoniae. We attempted to correlate postvaccination serum serotype-specific pneumococcal anticapsular immunoglobulin (Ig) G concentrations with new acquisitions of vaccine-type (VT) serotypes and the VT-related serotype 6A. A total of 132 day care center attendees aged 12-35 months received a 9-valent PCV (PnCRM9) and were followed for 2 years for new nasopharyngeal acquisitions of S. pneumoniae. A total of 132 control subjects received a meningococcus type C conjugate vaccine. Serum serotype-specific pneumococcal anticapsular IgG concentrations were determined at 1 month after complete immunization. A logistic...

...acquisition, and achieved statistical significance for serotypes 14 and 19F. Similarly, a new acquisition of serotype 6A was shown to be significantly inversely related to the anti-6B IgG concentration. An...

6/3,K/3 (Item 3 from file: 24)
DIALOG(R)File 24:CSA Life Sciences Abstracts

0002213504 IP ACCESSION NO: 5123885
The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, Part II

Hausdorff, WP; Bryant, J; Kloek, C; Paradiso, PR; Siber, GR
Wyeth-Lederle Vaccines, West Henrietta and Pearl River, New York, USA

Clinical Infectious Diseases, v 30, n 1, p 122-140, January 2000
PUBLICATION DATE: 2000

DOCUMENT TYPE: Journal Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English
ISSN: 1058-4838
FILE SEGMENT: Bacteriology Abstracts (Microbiology B)

Hausdorff, WP; Bryant, J; Kloek, C; Paradiso, PR; Siber, GR

ABSTRACT:
... slightly less frequently from CSF than from blood or MEF. Nonetheless, serogroups in the 9-valent conjugate vaccine formulation still comprised approximately 75% of pneumococcal isolates from the CSF of young ...

6/3,K/4 (Item 4 from file: 24)
DIALOG(R)File 24:CSA Life Sciences Abstracts

0002213503 IP ACCESSION NO: 5123884
Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, Part I

Hausdorff, WP; Bryant, J; Paradiso, PR; Siber, GR
Wyeth-Lederle Vaccines, West Henrietta and Pearl River, New York, USA

Clinical Infectious Diseases, v 30, n 1, p 100-121, January 2000

PUBLICATION DATE: 2000

DOCUMENT TYPE: Journal Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English
ISSN: 1058-4838
FILE SEGMENT: Bacteriology Abstracts (Microbiology B)

Hausdorff, WP; Bryant, J; Paradiso, PR; Siber, GR

ABSTRACT:
... young children and older children/adults, respectively, in each geographic region. Serogroups in the 7-valent formulation (4, 6, 9, 14, 18, 19, and 23) cause 70%-88% of IPD in...

...Oceania, Africa, and Europe, and <65% in Latin America and Asia. Serogroups in the 9-valent formulation (7-valent + 1,5) cause 80%-90% of IPD in each region except Asia (66%). Serogroup 1...

...and Canada and Oceania. In contrast, several serogroups not found in 7-, 9-, and 11-valent conjugate formulations are significant causes of disease in older children/adults. Nevertheless, each conjugate formulation ...

6/3,K/5 (Item 5 from file: 24)

0001884177 IP ACCESSION NO: 4355555
Minimum protective serum concentrations of pneumococcal anti-capsular antibodies in infant rats

Stack, AM; Malley, R; Thompson, CM; Kobzik, L; Siber, GR; Saladino, RA*
Division of Emergency Medicine, Children's Hospital, 300 Longwood Ave., Boston, MA 02115, USA, [mailto:saladino@a1.tch.harvard.edu]

Journal of Infectious Diseases, v 177, n 4, p 986-990, April 1998
PUBLICATION DATE: 1998

DOCUMENT TYPE: Journal Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English
ISSN: 0022-1899
FILE SEGMENT: Bacteriology Abstracts (Microbiology B)

Stack, AM; Malley, R; Thompson, CM; Kobzik, L; Siber, GR; Saladino, RA*

ABSTRACT:
... a statistically significant reduction in mortality compared with the reduction in untreated controls, except for serotype 14, which required 2.32 mu g/mL for a significant reduction in mortality. The...

6/3,K/6 (Item 6 from file: 24)

0000532782 IP ACCESSION NO: 1443511
Antibody response to pretreatment immunization and post-treatment boosting with bacterial polysaccharide vaccines in patients with Hodgkin's disease.

Siber, GR; Gorham, C; Martin, P; Corkery, JC; Schiffman, G
Div. Infect. Dis., Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA 02115, USA

Annals of Internal Medicine, v 104, n 4, p 467-475, 1986
ADDL. SOURCE INFO: Annals of Internal Medicine [ANN. INTERN. MED.], vol. 104, no. 4, pp. 467-475, 1986
PUBLICATION DATE: 1986

DOCUMENT TYPE: Journal Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English
ISSN: 0003-4819
FILE SEGMENT: Bacteriology Abstracts (Microbiology B); Immunology Abstracts ; Industrial & Applied Microbiology Abstracts (Microbiology A)
Siber, GR; Gorham, C; Martin, P; Corkery, JC; Schiffman, G

ABSTRACT:
... splenectomy in Hodgkin's disease. To define an optimal immunization strategy, 51 patients received 14-valent pneumococcal, Haemophilus influenzae type b, and meningococcal group C vaccines therapy and 2 to 12 ...

6/3,K/7 (Item 7 from file: 24)
DIALOG(R)File 24:CSA Life Sciences Abstracts

0000282257 IP ACCESSION NO: 750386
Preparation of human hyperimmune globulin to Haemophilus influenzae b, Streptococcus pneumoniae , and Neisseria meningitidis .

Siber, GR; Ambrosino, DM; McIver, J; Ervin, TJ; Schiffman, G; Sallan, S; Grady, GF
Dep. Med., Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA 02115, USA

Infection and Immunity, v 45, n 1, p 248-254, 1984
ADDL. SOURCE INFO: Infection and Immunity [INFECT. IMMUN.], vol. 45, no. 1, pp. 248-254, 1984
PUBLICATION DATE: 1984

DOCUMENT TYPE: Journal Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English
ISSN: 0019-9567
FILE SEGMENT: Bacteriology Abstracts (Microbiology B); Immunology Abstracts
Siber, GR; Ambrosino, DM; McIver, J; Ervin, TJ; Schiffman, G; Sallan, S; Grady, GF

ABSTRACT:
... encapsulated bacteria, the authors have immunized healthy adults with H. influenzae type b vaccine, 14-valent pneumococcal vaccine, and meningococcal group A and C vaccine; collected plasma by repeated pheresis;

and...

6/3,K/8 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

149582415 CA: 149(26)582415p PATENT
Multivalent pneumococcal polysaccharide-protein conjugate composition
INVENTOR(AUTHOR): Hausdorff, William P.; Siber, George Rainer; Paradiso, Peter R.; Prasad, A. Krishna
LOCATION: USA
ASSIGNEE: Wyeth, John, and Brother Ltd.
PATENT: PCT International ; WO 2008143709 A2 DATE: 20081127
APPLICATION: WO 2007US86941 (20071210) *US 2006644924 (20061222)
PAGES: 59pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
IPCR/8 + Level Value Position Status Version Action Source Office:
A61K-0039/00 A I F B 20060101 H EP
A61P-0035/00 A I L B 20060101 H EP
DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BH; BR; BW; BY; BZ; CA; CH; CN; CO; CR; CU; CZ; DE; DK; DM; DO; DZ; EC; EE; EG; ES; FI; GB; GD; GE; GH; GM; GT; HN; HR; HU; ID; IL; IN; IS; JP; KE; KG; KM; KN; KP; KR; KZ; LA; LC; LK; LR; LS; LT; LU; LY; MA; MD; ME; MG; MK; MN; MW; MX; MY; MZ; NA; NG; NI; NO; NZ; OM; PG; PH; PL; PT; RO; RS; RU; SC; SD; SE; SG; SK; SL; SM; SV; SY; TJ; TM; TN; TR; TT; TZ DESIGNATED REGIONAL: AT; BE; BG; CH ; CY; CZ; DE; DK; EE; ES; FI; FR; GB; GR; HU; IE; IS; IT; LT; LU; LV; MC; MT; NL; PL; PT; RO; SE; SI; SK; TR; BF; BJ; CF; CG; CI; CM; GA; GN; GQ; GW; ML; MR; NE; SN; TD; TG; BW; GH; GM; KE; LS; MW; MZ; NA; SD; SL; SZ; TZ; UG; ZM; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM

6/3,K/9 (Item 1 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00104017

Prevention Of Haemophilus Influenzae Type B Infections In High-Risk Infants Treated With Bacterial Polysaccharide Immune Globulin (Original Article)

Santosham, Mathuram; Reid, Raymond; Ambrosino, Donna M.; Wolff, Mark C., Ph.D.; Almeido-Hill, Janne, B.S.; Priehs, Claudette, B.S.; Aspery, Kathy M., R.N.; Garrett, Steve, R.Ph.; Croll, Larry, R.Ph.; Foster, Stephan, Pharm.D.; Burge, Gerald, R.Ph.; Page, Peter; Zacher, Bonnie, L.P.N.; Moxon, Richard, M.B., B.Chir., F.R.C.P.; Siber, George R. Siber
The New England Journal of Medicine
October 8, 1987; 317 (15),pp 923-929
LINE COUNT: 00506 WORD COUNT: 06991

...Zacher, Bonnie, L.P.N.; Moxon, Richard, M.B., B.Chir., F.R.C.P.; Siber, George R. Siber

TEXT
...had otitis media, and one had no focus of infection. Three of the infants had serotype 4 pneumococcus, and one had serotype 18.
The two cases of pneumococcal infection in the BPIG group occurred 105 and 121...

...not have an identifiable focus of infection. The pneumococcus from one of these patients was serotype 4, and that from the other patient was

```
not serotyped.
     Minor Outcomes (Table 4) *Table...
? e au=paradiso, p?

Ref   Items  Index-term
E1        7  AU=PARADISO, P.
E2       27  AU=PARADISO, P. R.
E3        0 *AU=PARADISO, P?
E4        6  AU=PARADISO, PETER
E5        4  AU=PARADISO, PETER R
E6       33  AU=PARADISO, PETER R.
E7        1  AU=PARADISO, PETER ROCCO
E8       31  AU=PARADISO, PR
E9        2  AU=PARADISO, R
E10     123  AU=PARADISO, R.
E11       2  AU=PARADISO, R. A.
E12       2  AU=PARADISO, R. L.

          Enter P or PAGE for more
? s e1-6
>>>Term "6" in invalid position
? s e1-e6
               7  AU=PARADISO, P.
              27  AU=PARADISO, P. R.
               0  AU=PARADISO, P?
               6  AU=PARADISO, PETER
               4  AU=PARADISO, PETER R
              33  AU=PARADISO, PETER R.
      S7      77  E1-E6
? s s7 and (serotype or valent)
              77  S7
          207443  SEROTYPE
           58798  VALENT
      S8      18  S7 AND (SEROTYPE OR VALENT)
? rd

>>>Duplicate detection is not supported for File 393.

>>>Duplicate detection is not supported for File 391.

>>>Records from unsupported files will be retained in the RD set.
      S9      13  RD  (unique items)
? t s9/3,k/1-13
>>>KWIC option is not available in file(s): 399

 9/3,K/1     (Item 1 from file: 24)
DIALOG(R)File  24:CSA Life Sciences Abstracts
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0003095955       IP ACCESSION NO: 7640697
Estimating the protective concentration of anti-pneumococcal capsular
polysaccharide antibodies

Siber, George R;  Chang, Ih;  Baker, Sherryl;  Fernsten, Philip;  O'Brien,
Katherine L;  Santosham, Mathuram;  Klugman, Keith P;  Madhi, Shabir A;
Paradiso, Peter;  Kohberger, Robert
Wyeth Vaccines Research, Pearl River, New York, USA,
[mailto:siberg@wyeth.com]

Vaccine, v 25, n 19, p 3816-3826, May 2007
PUBLICATION DATE: 2007

PUBLISHER: Elsevier Science, The Boulevard Langford Lane Kidlington Oxford
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OX5 1GB UK, [mailto:usinfo-f@elsevier.com], [URL:http://www.elsevier.nl]

DOCUMENT TYPE: Journal Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English
ISSN: 0264-410X
FILE SEGMENT: Bacteriology Abstracts (Microbiology B); Immunology Abstracts

...Sherryl; Fernsten, Philip; O'Brien, Katherine L; Santosham, Mathuram; Klugman, Keith P; Madhi, Shabir A; Paradiso, Peter; Kohberger, Robert

ABSTRACT:
... e. absorption with 22F pneumococcal polysaccharide, which increases the specificity of the assay for vaccine serotype anticapsular antibodies by removing non-specific antibodies. Using sera from infants in the pivotal efficacy...

9/3,K/2 (Item 1 from file: 98)
DIALOG(R)File 98:General Sci Abs
(c) 2009 The HW Wilson Co. All rts. reserv.

04652943 H.W. WILSON RECORD NUMBER: BGSA01152943
Geographical differences in invasive pneumococcal disease rates and serotype frequency in young children.
Hausdorff, William P
Siber, George; Paradiso, Peter R
Lancet (North American edition) (Lancet) v. 357 no9260 (Mar. 24 2001) p. 950-2
SPECIAL FEATURES: bibl f graph ISSN: 0099-5355
LANGUAGE: English
COUNTRY OF PUBLICATION: United States

Geographical differences in invasive pneumococcal disease rates and serotype frequency in young children.
Siber, George; Paradiso, Peter R

...ABSTRACT: the more than 90 pneumococcal serotypes are most likely to cause invasive pneumococcal disease (IPD). Serotype distribution is thought to vary geographically, even between regions as socioeconomically similar as western Europe...

...probably underdiagnosed and under-reported in western Europe. On the basis of a comparison of serotype distributions between the two regions, we also postulate that those serotypes found at similar frequencies...

9/3,K/3 (Item 1 from file: 162)
DIALOG(R)File 162:Global Health
(c) 2009 CAB International. All rts. reserv.

0005470369 CAB Accession Number: 20093106959
Immunology of combining CRM SUB 197 conjugates for Streptococcus pneumoniae , Neisseria meningitis and Haemophilus influenzae in Chilean infants.
Lagos, R.; Munoz, A.; Levine, M. M.; Watson, W.; Chang, I.; Paradiso, P.
Author email address: rosanna.lagos@adsl.tie.cl
Centro para Vacunas en Desarrollo-Chile, Hospital de Ninos Roberto del Rio (4 SUP o Piso), Servicio de Salud Metropolitano Norte, Avenida Zanartu

1085, Independencia - Santiago, Chile.
Vaccine vol. 27 (17): p.2299-2305
Publication Year: 2009
ISSN: 0264-410X
Digital Object Identifier: 10.1016/j.vaccine.2009.02.022
Publisher: Elsevier Amsterdam, Netherlands
Language: English
Record Type: Abstract
Document Type: Journal article

We evaluated the immunogenicity and safety of an investigational combination of 9-valent pneumococcal conjugate vaccine (PCV9) and meningococcal group C conjugate (MnCC) vaccine (PCV9-MnCC) administered concomitantly...

Lagos, R.; Munoz, A.; Levine, M. M.; Watson, W.; Chang, I.; Paradiso, P.

9/3,K/4 (Item 2 from file: 162)
DIALOG(R)File 162:Global Health

0004801664 CAB Accession Number: 20013029720
Safety and immunogenicity of four doses of Neisseria meningitidis group C vaccine conjugated to CRM SUB 197 in United States infants.
Rennels, M. B.; Edwards, K. M.; Keyserling, H. L.; Reisinger, K.; Blatter, M. M.; Quataert, S. A.; Madore, D. V.; Chang Ih; Malinoski, F. J.; Hackell, J. G.; Paradiso, P. R.
Department of Pediatrics, Center for Vaccine Development, University of Maryland School of Medicine, Baltimore, Maryland, USA.
Pediatric Infectious Disease Journal vol. 20 (2): p.153-159
Publication Year: 2001
ISSN: 0891-3668
Digital Object Identifier: 10.1097/00006454-200102000-00007
Publisher: Lippincott Williams & Wilkins Hagerstown, USA
Language: English
Record Type: Abstract
Document Type: Journal article

... randomized, controlled double blind study; children in the other treatment arm were given a 7-valent conjugate pneumococcal vaccine. Parents reenrolled 64 of these children at 12 to 15 months to...

...M.; Quataert, S. A.; Madore, D. V.; Chang Ih; Malinoski, F. J.; Hackell, J. G.; Paradiso, P. R.

9/3,K/5 (Item 3 from file: 162)
DIALOG(R)File 162:Global Health

0004760741 CAB Accession Number: 20002009737
The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, part II.
Hausdorff, W. P.; Bryant, J.; Kloek, C.; Paradiso, P. R.; Siber, G. R.
Wyeth-Lederle Vaccines, 211 Bailey Road, West Henrietta, NY 14586, USA.
Clinical Infectious Diseases vol. 30 (1): p.122-140
Publication Year: 2000
ISSN: 1058-4838
Digital Object Identifier: 10.1086/313609
Language: English

Record Type: Abstract
Document Type: Journal article

... slightly less frequently from CSF than from blood or MEF. Nonetheless, serogroups in the 9-valent conjugate vaccine formulation still comprised ~75% of pneumococcal isolates from the CSF of young children...

Hausdorff, W. P.; Bryant, J.; Kloek, C.; Paradiso, P. R.; Siber, G. R.

9/3,K/6 (Item 4 from file: 162)
DIALOG(R)File 162:Global Health

0004759495 CAB Accession Number: 20002009318
Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I.
Hausdorff, W. P.; Bryant, J.; Paradiso, P. R.; Siber, G. R.
Wyeth-Lederle Vaccines, 211 Bailey Road, West Henrietta, NY 14586, USA.
Clinical Infectious Diseases vol. 30 (1): p.100-121
Publication Year: 2000
ISSN: 1058-4838
Digital Object Identifier: 10.1086/313608
Language: English
Record Type: Abstract
Document Type: Journal article

... young children and older children/adults, respectively, in each geographic region. Serogroups in the 7-valent formulation (4, 6, 9, 14, 18, 19, and 23) cause 70%-88% of IPD in...

... Oceania, Africa, and Europe, and <65% in Latin America and Asia. Serogroups in the 9-valent formulation (7-valent + 1, 5) cause 80%-90% of IPD in each region except Asia (66%). Serogroup 1...
...and Canada and Oceania. In contrast, several serogroups not found in 7-, 9-, and 11-valent conjugate formulations are significant causes of disease in older children/adults. Nevertheless, each conjugate formulation ...

Hausdorff, W. P.; Bryant, J.; Paradiso, P. R.; Siber, G. R.

9/3,K/7 (Item 5 from file: 162)
DIALOG(R)File 162:Global Health

0004752973 CAB Accession Number: 20002006998
Safety and immunogenicity of heptavalent pneumococcal CRM SUB 197 conjugate vaccine in infants and toddlers.
Shinefield, H. R.; Black, S.; Ray, P.; Chang Ih; Lewis, N.; Fireman, B.; Hackell, J.; Paradiso, P. R.; Siber, G.; Kohberger, R.; Madore, D. V.; Malinowski, F. J.; Kimura, A.; Le Chinh; Landaw, I.; Aguilar, J.; Hansen, J.
Kaiser Permanente, Vaccine Study Center, 4131 Geary Blvd., San Francisco, CA 94118, USA.
Pediatric Infectious Disease Journal vol. 18 (9): p.757-763
Publication Year: 1999
ISSN: 0891-3668
Digital Object Identifier: 10.1097/00006454-199909000-00004
Language: English
Record Type: Abstract

Document Type: Journal article

... After the third dose of PNCRM7 geometric mean concentrations (GMCs) ranged from 1.01 for serotype 9V to 3.72 microg/ml for serotype 14. More than 90% of all subjects had a post-third dose titre of >=0...
... in a near conventional threshold for statistical significance of a post-Dose 4 GMC for serotype 23F [alone 6.75 microg/ml vs. concurrent 4.11 microg/ml (P =0.057...

Shinefield, H. R.; Black, S.; Ray, P.; Chang Ih; Lewis, N.; Fireman, B.; Hackell, J.; Paradiso, P. R.; Siber, G.; Kohberger, R.; Madore, D. V. ; Malinowski, F. J.; Kimura, A.; Le...

9/3,K/8 (Item 6 from file: 162)
DIALOG(R)File 162:Global Health

0004683637 CAB Accession Number: 19982008802
Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM SUB 197 in United States infants.
Rennels, M. B.; Edwards, K. M.; Keyserling, H. L.; Reisinger, K. S.; Hogerman, D. A.; Madore, D. V.; Chang, I.; Paradiso, P. R.; Malinoski, F. J.; Kimura, A.
Center for Vaccine Development and Department of Pediatrics, University of Maryland School of Medicine, Baltimore, MD, USA.
Pediatrics vol. 101 (4): p.604-611
Publication Year: 1998
ISSN: 0031-4005
Language: English
Record Type: Abstract
Document Type: Journal article

... administered concurrently. All 7 vaccine serotypes were immunogenic. The kinetics of the immune responses were serotype-specific. After 3 doses of PNCRM7, between 92% to 100% of children had >=0.15...

...M.; Keyserling, H. L.; Reisinger, K. S.; Hogerman, D. A.; Madore, D. V. ; Chang, I.; Paradiso, P. R.; Malinoski, F. J.; Kimura, A.

9/3,K/9 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

149582415 CA: 149(26)582415p PATENT
Multivalent pneumococcal polysaccharide-protein conjugate composition
INVENTOR(AUTHOR): Hausdorff, William P.; Siber, George Rainer; Paradiso, Peter R.; Prasad, A. Krishna
LOCATION: USA
ASSIGNEE: Wyeth, John, and Brother Ltd.
PATENT: PCT International ; WO 2008143709 A2 DATE: 20081127
APPLICATION: WO 2007US86941 (20071210) *US 2006644924 (20061222)
PAGES: 59pp. CODEN: PIXXD2 LANGUAGE: English
PATENT CLASSIFICATIONS:
IPCR/8 + Level Value Position Status Version Action Source Office:
A61K-0039/00 A I F B 20060101 H EP
A61P-0035/00 A I L B 20060101 H EP
DESIGNATED COUNTRIES: AE; AG; AL; AM; AT; AU; AZ; BA; BB; BG; BH; BR; BW; BY; BZ; CA; CH; CN; CO; CR; CU; CZ; DE; DK; DM; DO; DZ; EC; EE; EG; ES; FI; GB; GD; GE; GH; GM; GT; HN; HR; HU; ID; IL; IN; IS; JP; KE; KG; KM; KN; KP; KR; KZ; LA; LC; LK; LR; LS; LT; LU; LY; MA; MD; ME; MG; MK; MN; MW; MX; MY;

MZ; NA; NG; NI; NO; NZ; OM; PG; PH; PL; PT; RO; RS; RU; SC; SD; SE; SG; SK; SL; SM; SV; SY; TJ; TM; TN; TR; TT; TZ DESIGNATED REGIONAL: AT; BE; BG; CH ; CY; CZ; DE; DK; EE; ES; FI; FR; GB; GR; HU; IE; IS; IT; LT; LU; LV; MC; MT; NL; PL; PT; RO; SE; SI; SK; TR; BF; BJ; CF; CG; CI; CM; GA; GN; GQ; GW; ML; MR; NE; SN; TD; TG; BW; GH; GM; KE; LS; MW; MZ; NA; SD; SL; SZ; TZ; UG; ZM; ZW; AM; AZ; BY; KG; KZ; MD; RU; TJ; TM

9/3,K/10 (Item 1 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

04113189 SUPPLIER NUMBER: 196390566 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Immunology of combining CRM.sub.197 conjugates for Streptococcus pneumoniae, Neisseria meningitis and Haemophilus influenzae in Chilean infants.(Report)
Lagos, Rosanna; Munoz, Alma; Levine, Myron M.; Watson, Wendy; Chang, Ih; Paradiso, Peter
Vaccine, 27, 17, 2299(7)
April 14,
2009
DOCUMENT TYPE: Report PUBLICATION FORMAT: Magazine/Journal ISSN: 0264-410X LANGUAGE: English RECORD TYPE: Abstract TARGET AUDIENCE: Academic

...Paradiso, Peter

...AUTHOR ABSTRACT: Combination vaccines
Abstract:
We evaluated the immunogenicity and safety of an investigational combination of 9-valent pneumococcal conjugate vaccine (PCV9) and meningococcal group C conjugate (MnCC) vaccine (PCV9-MnCC) administered concomitantly...

9/3,K/11 (Item 2 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

02011727 SUPPLIER NUMBER: 77032076 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Geographical differences for pneumococcal disease.(Brief Article)(Letter to the Editor)
Paradiso, Peter R; Siber, George; Hausdorff, William P; Linares, Josefina; Tubau, Fe; Moreno, Georgina; Pallares, Roman
The Lancet, 358, 9279, 419
August 4,
2001
DOCUMENT TYPE: Brief Article; Letter to the Editor PUBLICATION FORMAT: Magazine/Journal; Refereed ISSN: 0099-5355 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 1318 LINE COUNT: 00111

Paradiso, Peter R...
... countries such as the UK, Germany, Denmark, and Finland.(2)
The spread of a resistant serotype can occur among young children (eg, in day-care centres)(3) and adults (eg, in...

...are probably similar, or even worse, than those made in the other western European countries.
Serotype distribution may vary over time. Thus, in our hospital for adult patients, from 1979 to...

...in clinical practice and patients' characteristics, the spread of resistant clones may produce variations in serotype distribution, and should be taken into account in planning vaccination strategies.
(*) Roman Pallares, Georgina Moreno...

...es)
(1) Hausdorff WP, Siber G, Paradiso PR. Geographical differences in invasive pneumococcal disease and serotype frequency in young children. Lancet 2001; 357: 950-52.
(2) Sankilampi U, Herva E, Haikula...

...of antibiotic resistance in a given population could potentially have an important impact on the serotype distribution.
However, we do not agree with their assertion that the distribution of serotypes causing...

...study, around 74% of IPD-causing serogroups in Spanish children were represented in the 7-valent conjugate vaccine formulation (4, 6, 9, 14, 19, 23), and serotypes 1 and 5 accounted...

...in line with most studies from western Europe, and contrast with the 85-90% 7-valent serogroup coverage range consistently reported for US and Canadian studies, with serotypes 1 and 5...

...suggest that this factor is crucial for determining serogroup distribution in that country. However, 7-valent serogroup coverage for IPD in Spanish children younger than 5 years (78%)(1) is similar...

...but only 63% in those aged 2-5 years, were serogroups represented in the 7-valent formulation. Similar striking differences between those

9/3,K/12 (Item 3 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

01979670 SUPPLIER NUMBER: 72341085 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Geographical differences in invasive pneumococcal disease rates and serotype frequency in young children.(Hypothesis)
Hausdorff, William P; Siber, George; Paradiso, Peter R
The Lancet, 357, 9260, 950
March 24,
2001
PUBLICATION FORMAT: Magazine/Journal; Refereed ISSN: 0099-5355
LANGUAGE: English RECORD TYPE: Fulltext; Abstract TARGET AUDIENCE: Professional
WORD COUNT: 2671 LINE COUNT: 00223

Geographical differences in invasive pneumococcal disease rates and serotype frequency in young children.(Hypothesis)
...Paradiso, Peter R

TEXT:
...the more than 90 pneumococcal serotypes are most likely to cause invasive pneumococcal disease (IPD). Serotype distribution is thought to vary geographically, even between regions as socioeconomically similar as western Europe...
...probably underdiagnosed and under-reported in western Europe. On the basis of a comparison of serotype distributions between the two regions, we also postulate that those serotypes found at similar frequencies...
... this variation is the difference between western Europe and North America; a recently licensed 7-valent conjugate vaccine reportedly

covers 68-81% of serogroups in young children in western Europe, and...

...that a considerable proportion of mild IPD is normally unrecognised.(15)
Regional differences in IPD serotype distribution are skewed by differences in the patient populations sampled. If some serotypes or serogroups...

...have ratios near to 1, suggesting that they mainly cause severe IPD. Thus, even though serotype 1 causes 5% of IPD in western Europe and only 0.5% in the USA, the rates of serotype 1 disease in these regions are each about 0.9 per 100000 children/year. The...are rare.
To what extent might differences in local blood-culture practices affect interpretation of serotype results in other contexts? In some regions the willingness to take a blood sample depends on the age of the child, which complicates cross-study comparisons of serotype distribution in paediatric populations with different age distributions. From a historical perspective, interpretation of changes in serotype distribution since the 1930s in the USA needs to take into account increases in the...
...include in a vaccine.
Hypothesis
We suggest that a large proportion of geographical variation in serotype distribution is attributable to differences in selection of patients and blood-culture practices. However, some true regional variations in serotype prevalence--eg, serotype 21--probably exist, especially outside the USA and Europe.
Testing the hypothesis
Direct testing of our hypothesis would require a prospective investigation of serotype monitoring and IPD rates in several countries, in which precise ages, disease manifestations, and blood...

...world could substantially affect the perceived coverage of multivalent pneumococcal-conjugate vaccines. The new 7-valent vaccine might prevent a greater proportion of overall IPD burden in European and Latin American...

...they are prescribed antibiotics before diagnosis. Conversely, if certain serotypes not contained in the 7-valent vaccine are disproportionately responsible for severe disease, this vaccine might prevent a slightly smaller proportion...1998; 30: 257-62.
(20) Butler JC, Breiman RF, Lipman HB, Hofmann J, Facklam RR. Serotype distribution of Streptococcus pneumoniae infections among preschool children in the United States, 1978-1994: implications...

...Drug Resist 1997; 3: 111-15.
(27) Scott JAG, Hall AJ, Hannington A, et al. Serotype distribution and prevalence of resistance to benzylpenicillin in three representative populations of Streptococcus pneumoniae isolates...

9/3,K/13 (Item 4 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

01766556 SUPPLIER NUMBER: 20605969 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM197 in United States infants.
Rennels, MArgaret B.; Edwards, Kathryn M.; Keyserling, Harry L.; Reisinger, Keith S.; Hogerman, Deborah A.; Madore, Dace V.; Chang, Ih; Paradiso, Peter R.; Malinowski, Frank J.; Kimura, Alan
Pediatrics, v101, n4, p604(8)
April,
1998

PUBLICATION FORMAT: Magazine/Journal ISSN: 0031-4005 LANGUAGE: English
RECORD TYPE: Abstract TARGET AUDIENCE: Professional

...Paradiso, Peter R

...AUTHOR ABSTRACT: administered concurrently. All 7 vaccine serotypes were immunogenic. The kinetics of the immune responses were serotype -specific. After three doses of PNCRM7, between 92% to 100% of children had 20.15...

```
? s serotype and (6A)
          207443  SEROTYPE
          120097  6A
     S10    1964  SEROTYPE AND (6A)
? s serotype and pneum?
          207443  SEROTYPE
         1631879  PNEUM?
     S11   26417  SEROTYPE AND PNEUM?
? s s11 and (conjugat?)
           26417  S11
         1255384  CONJUGAT?
     S12    7610  S11 AND (CONJUGAT?)
? s s12 and (1 and 3 and 4 and 5 and 6A and 6B and 7f and 9v and 14 and 18c and 19A
and 23f)
Processing
Processed  20 of  50 files ...
Completed processing all files
           7610  S12
       51656233  1
       41794772  3
       33530216  4
       32482497  5
         120097  6A
          61534  6B
           8341  7F
           6071  9V
        7126896  14
           5317  18C
           8400  19A
           7373  23F
     S13      58  S12 AND (1 AND 3 AND 4 AND 5 AND 6A AND 6B AND 7F AND 9V
                  AND 14 AND 18C AND 19A AND 23F)
? rd

>>>Duplicate detection is not supported for File 393.

>>>Duplicate detection is not supported for File 391.

>>>Records from unsupported files will be retained in the RD set.
     S14      38  RD  (unique items)
? t s14/3,k/1-38
>>>KWIC option is not available in file(s): 399

 14/3,K/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2009 The Thomson Corporation. All rts. reserv.
```

17968089   BIOSIS NO.: 200400338878
Clinical features, aetiology and outcome of empyema in children in the north east of England
AUTHOR: Eastham K M; Freeman R; Kearns A M; Eltringham G; Clark J; Leeming J; Spencer D A (Reprint)
AUTHOR ADDRESS: Dept Resp Paediat, Freeman Rd Hosp, Newcastle Upon Tyne, Tyne and Wear, NE7 7DN, England**England

AUTHOR E-MAIL ADDRESS: spencer@nuth.northy.nhs.uk
JOURNAL: Thorax 59 (6): p522-525 June 2004 2004
MEDIUM: print
ISSN: 0040-6376
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

...ABSTRACT: pleural fluid was performed for 47 cases. Forty three pleural fluid specimens, culture negative for pneumococcus, were analysed for pneumococccal DNA by real time polymerase chain reaction (PCR). Penicillin susceptibility was determined for DNA positive specimens using complementary PCR assay. Capsular serotype specific antigen detection was by enzyme immunoassay (EIA) using monoclonal antibodies to serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. Clinical data were obtained from patient notes, supplemented by a postal questionnaire. Results: The median (range) age of the patients was 5.6 (0.6-16.9) years and 70% were male. The median (range) duration of illness before referral to hospital was 5 (0-25) days. Forty five (96%) had received antibiotics before referral; 32 (68%) required decortication and eight (21%) thoracocentesis. Median postoperative stay was 4 days (2-8). Thirty two (75%) pneumococcal culture negative specimens were pneumococcal DNA positive; 17 (53%) of these were serotype 1. All were penicillin sensitive. Conclusions: Pneumococcus is the major pathogen in childhood empyema and serotype 1 is the prevalent serotype. This has implications for vaccine development and immunisation strategy as the current 7-valent pneumococcal conjugate vaccine does not protect against serotype 1.

DESCRIPTORS:
  ORGANISMS: Streptococcus pneumoniae {pneumococcus}
    (Gram-Positive Cocci...

...penicillin sensitive, serovar-1, serovar-14, serovar-18C, serovar-19A, serovar-19F, serovar-23F, serovar-3, serovar-4, serovar-5, serovar-6A, serovar-6B, serovar-7F, serovar-9V;
  CHEMICALS & BIOCHEMICALS: 7-valent pneumococcal conjugate vaccine...

14/3,K/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

17654903 BIOSIS NO.: 200400025660
Serotype and antimicrobial susceptibility of Streptococcus pneumoniae recovered from invasive disease in Portugal (1999-2002).
AUTHOR: Dias R (Reprint); Louro D (Reprint); Gemvsa (Reprint); Canica M (Reprint)
AUTHOR ADDRESS: NIH Dr. Ricardo Jorge, Lisbon, Portugal**Portugal
JOURNAL: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 43 p133 2003 2003
MEDIUM: print
CONFERENCE/MEETING: 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy Chicago, IL, USA September 14-17, 2003; 20030914
SPONSOR: American Society for Microbiology
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

Serotype and antimicrobial susceptibility of Streptococcus pneumoniae recovered from invasive disease in Portugal (1999-2002).

ABSTRACT: Background: Streptococcus pneumoniae (Sp) is one of the most common bacteria causing invasive diseases in Portugal. The aim of this study was to evaluate the serotype-susceptibility relationship in invasive S. p. in Portugal. Methods: 614 consecutive isolates were collected in...

...and 71% from adults. MICs to 9 antibiotics were determined by agar dilution method (NCCLS). Serotype was performed by Dot-Blot and Quellung reaction. Sequence type (ST) was determined by MLST. Results: MIC90 (mg/L) ranged as follow between 1999 and 2002: 0.5-0.8 to penicillin-Pen, 0.25-0.5 to cefotaxime-Ctx, 0.5 to ceftriaxone-Ctr, 0.5-32 to tetracycline-Tet, 4-8 to erythromycin-Ery, 0.125-16 to clindamycin-Cli, 4 to chloramphenicol-Cm, 2 to ofloxacin-Of and 1-2 to ciprofloxacin-Cip. Serotypes 14, 1, 3, 8, 23F, 6B, 4, 9V, 19F, 7F, 6A and 9N (in descending order) represented 80% of invasive isolates. Serotypes 1, 14, 3 and 4 were more frequent in blood and serotypes 23F, 19F and 11 in CSF. Serotypes 14, 1, 6B, 23F, 7F, 19F, 9V and 3 (in descending order) were the most frequent in children. Serotypes 3, 1, 14, 8, 4, 9V, 23F, 19F, 6B, 7F, 9N, 6A, 18C and 19A (in descending order) were more frequent in adults. We detected 4 principal ST (ST156, ST143, ST15 and ST9) among 26 Ery resistant strains with serotype 14. Conclusions: Our results suggest that the new heptavalent conjugate vaccine against S. p. cover 44% of invasive S. p. serotypes in the studied population...

DESCRIPTORS:
ORGANISMS: Streptococcus pneumoniae (Gram-Positive Cocci...

...pathogen, sequence type 143, sequence type 15, sequence type 156, sequence type 9, serotype 1, serotype 11, serotype 14, serotype 18C, serotype 19A, serotype 19F, serotype 23F, serotype 3, serotype 4, serotype 6A, serotype 6B, serotype 7F, serotype 8, serotype 9N, serotype 9V;
CHEMICALS & BIOCHEMICALS: ...heptavalent conjugate vaccine...
MISCELLANEOUS TERMS: ...serotype-susceptibility relationship
CONCEPT CODES:

14/3,K/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

17654888 BIOSIS NO.: 200400025645
Antibiotic susceptibility and serotype distribution of S. pneumoniae circulating in Italy during 2000-2002: Results of the SEMPRE surveillance Study.
AUTHOR: Schito G C (Reprint); Fadda G; Nicoletti G; Marchese A (Reprint)
AUTHOR ADDRESS: Inst. of Microbiology, Univ. of Genoa, Genoa, Italy**Italy
JOURNAL: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 43 p129 2003 2003
MEDIUM: print
CONFERENCE/MEETING: 43rd Annual Interscience Conference on Antimicrobial Agents and Chemotherapy Chicago, IL, USA September 14-17, 2003; 20030914
SPONSOR: American Society for Microbiology
DOCUMENT TYPE: Meeting; Meeting Abstract

RECORD TYPE: Abstract
LANGUAGE: English

Antibiotic susceptibility and serotype distribution of S. pneumoniae circulating in Italy during 2000-2002: Results of the SEMPRE surveillance Study.

ABSTRACT: Background: The strategies to combat S. pneumoniae infections include adequate antibiotic therapy and usage of prophylactic vaccines formulated on the basis of...

...Methods: In the SEMPRE study 20 centres during 2000-2002 have collected 1422 respiratory S. pneumoniae. Microorganisms were identified according to standard procedures. In vitro susceptibility to 9 antibiotics was determined...

...Statens Serum Institut, Copenhagen. Results: Total resistance to penicillin increased during the study period from 14.3 to 16. 1%. In 2002, for the first time in our Country, high-level (11. 3%) exceeded low-level resistance (4.8%). Similarly, an increase in macrolide-resistance was observed from 37.9% to 43.7...

...drugs (>99% susceptible strains) were: amoxicillin, amoxicillin/clavulanate, levofloxacin and rifampin followed by penicillin (85.5%), cefaclor (82.6%), tetracycline (69.2%) and clarithromycin (59.4%). The most frequent serotypes in descending order were 23F (17.0%), 3 (11.1%), 19F (9.3%), 6B (7. 4%), 19A (7%), 6A (5.0%), 9L (2.7%), 11L (2. 3%), 9V (2.1%), 7F, 9N and 18C (1.9% each). Conclusions: penicillin and macrolide resistance has increased in Italy during the last three...

...potency is extremely satisfactory. The most common serotypes found are those included in the eptavalent conjugate vaccine with the exception of serotype 3.

DESCRIPTORS:
ORGANISMS: S. pneumoniae {Streptococcus pneumoniae}
(Gram-Positive Cocci...

...pathogen, respiratory isolates, serotype 11L, serotype 18C, serotype 19A, serotype 19F, serotype 23F, serotype 3, serotype 6A, serotype 6B, serotype 7F, serotype 9L, serotype 9N, serotype 9V;
DISEASES: Streptococcus pneumoniae infection...
CHEMICALS & BIOCHEMICALS: ...heptavalent conjugate vaccine...
MISCELLANEOUS TERMS: ...serotype distribution
CONCEPT CODES:

14/3,K/4 (Item 1 from file: 24)
DIALOG(R)File 24:CSA Life Sciences Abstracts

0002646652 IP ACCESSION NO: 6077098
Assignment of Weight-Based Antibody Units for 13 Serotypes to a Human Antipneumococcal Standard Reference Serum, Lot 89-S(F)

Quataert, Sally A; Rittenhouse-Olson, Kate; Kirch, Carol S; Hu, Branda; Secor, Shelley; Strong, Nancy; Madore, Dace V
Wyeth Vaccines Research, Rochester. Departments of Biotechnical and Clinical Laboratory Sciences and Microbiology, The University at Buffalo,

State University of New York, Buffalo, New York

Clinical and Diagnostic Laboratory Immunology, v 11, n 6, p 1064-1069, November 2004
PUBLICATION DATE: 2004

PUBLISHER: American Society for Microbiology, 1752 N Street N.W. Washington, DC 20036 USA, [URL:http://www.asm.org/]

DOCUMENT TYPE: Journal Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English
ISSN: 1071-412X
FILE SEGMENT: Immunology Abstracts

ABSTRACT:
... antipneumococcal standard reference serum lot 89- S, also known as lot 89-SF, for Streptococcus pneumoniae capsular polysaccharide (PnPs) serotypes 2, 6A, 8, 9N, 10A, 11A, 12F, 15B, 19A, 17F, 20, 22F, and 33F, as well as for C-polysaccharide (C-Ps), extending the standard's usefulness for pneumococcal vaccine evaluation beyond the original serotype 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F assignments (S. A. Quataert, C. S. Kirch, L. J. Quackenbush Wiedl, D. C. Phipps, S...

...Skuse, and D. V. Madore, Clin. Diagn. Lab. Immunol. 2:590-597, 1995). The additional 14 assignments were determined using an equivalence of absorbance method with an anti-PnPs serotype 6B reference enzyme-linked immunosorbent assay (EIA). To assure accuracy, anti-PnPs EIA for serotype 14 antibodies, a previously assigned serotype, was performed concurrently. This method assures consistency of the new microgram-per-microliter assignments with...

...in lot 89-S agrees well with the separately determined total Ig assignment for each serotype. The lot 89-S assignments for serotypes 1, 5, 6B, 14, 18C, 19F, and 23F were used for pneumococcal conjugate vaccine clinical trial evaluation and to generate data in efficacy trials where serological correlates for protection have been proposed. The assignment of antibody concentrations to additional pneumococcal serotypes in this reference reagent facilitates the consistent and accurate comparison of serum antibody concentrations...

...DESCRIPTORS: trials; Vaccines; Immunoglobulin G; Immunoglobulin A; Enzyme-linked immunosorbent assay; Immunoglobulin M; Polysaccharides; Absorbance; Streptococcus pneumoniae

14/3,K/5 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

18193309 Genuine Article#: 337MY No. References: 17
Title: Identification of pneumococcal serotypes from culture-negative clinical specimens by novel real-time PCR
Author(s): Tarrago D (REPRINT) ; Fenoll A; Sanchez-Tatay D; Arroyo LA; Munoz-Almagro C; Esteva C; Hausdorff WP; Casal J; Obando I
Corporate Source: Inst Salud Carlos III,Ctr Nacl Microbiol, Serv Bacteriol, Spanish Reference Lab Pneumococci,Ctra Majadahonda Pozuelo Km 2/Madrid 28220//Spain/ (REPRINT); Inst Salud Carlos III,Ctr Nacl Microbiol, Serv Bacteriol, Spanish Reference Lab Pneumococci,Madrid 28220//Spain/; Hosp Univ Virgen Rocio,Fdn Reina Mercedes,Seville//Spain/; Hosp Univ Virgen

Rocio,Serv Infectol Pediat,Seville//Spain/; Hosp St Joan de Deu,Microbiol Serv,Barcelona//Spain/; GlaxoSmithKline Biol,Rixensart//Belgium/
Journal: CLINICAL MICROBIOLOGY AND INFECTION, 2008, V14, N9 (SEP), P828-834
ISSN: 1198-743X Publication date: 20080900
Publisher: BLACKWELL PUBLISHING, 9600 GARSINGTON RD, OXFORD OX4 2DQ, OXON, ENGLAND
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Title: Identification of pneumococcal serotypes from culture-negative clinical specimens by novel real-time PCR
Abstract: Pneumococcal parapneumonic empyema is an increasingly common complication in children. Conventional microbiological cultures indicate bacterial causes...

...diagnosis. The development and clinical evaluation of real-time PCR-based assays to detect the pneumococcal capsular wzg gene of all serotypes tested are reported here, and 24 of them have...

...target DNA sequences within the capsular polysaccharide gene cluster, it was possible to differentiate serotypes 1, 3, 5, 4, 6A, 6B, 7F/A, 8, 9V/A/N/L, 14, 15B/C, 18C/B, 19A, 19F/B/C, 23F and 23A. These assays showed high sensitivity (five to ten pneumococcal DNA equivalents) and they were validated with 175 clinical isolates of known serotypes. The clinical...

...88 culture-negative pleural fluids from children diagnosed with parapneumonic empyema in three Spanish hospitals. Pneumococcal DNA was detected in 87.5% of pleural fluids, and serotypes 1, 7F and 3 were responsible for 34.3%, 16. 4% and 11.9%, respectively, of cases of parapneumonic empyema in children. Such molecular methods are critical for the diagnosis of invasive pneumococcal disease and continued epidemiological surveillance in order to monitor serotype vaccine effectiveness.
...Identifiers--STREPTOCOCCUS-PNEUMONIAE; CONJUGATE VACCINE; EPIDEMIOLOGY; CARRIAGE; EMPYEMA; GENES

14/3,K/6 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

17461503 Genuine Article#: 263LT No. References: 26
Title: A rapid pneumococcal serotyping system based on monoclonal antibodies and PCR
Author(s): Yu J; Carvalho MDGS; Beall B; Nahm MH (REPRINT)
Corporate Source: Univ Alabama,Dept Pathol,845 19th St S,BBRB 614/Birmingham//AL/35294 (REPRINT); Univ Alabama,Dept Pathol,Birmingham//AL/35294; Ctr Dis Control & Prevent,Div Bacterial Dis,Atlanta//GA/30333
Journal: JOURNAL OF MEDICAL MICROBIOLOGY, 2008, V57, N2 (FEB), P171-178
ISSN: 0022-2615 Publication date: 20080200
Publisher: SOC GENERAL MICROBIOLOGY, MARLBOROUGH HOUSE, BASINGSTOKE RD, SPENCERS WOODS, READING RG7 1AG, BERKS, ENGLAND
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Title: A rapid pneumococcal serotyping system based on monoclonal antibodies and PCR
Abstract: Streptococcus pneumoniae expresses at least 91 different polysaccharide (PS) capsules and the currently available serotyping methods are tedious to perform. We have been developing a rapid pneumococcal serotyping assay (named the 'multibead assay') based

on the capacity of pneumococcal lysates to inhibit the ability of 24 different anti-capsule antibodies to bind to latex beads coated with 24 different PSs (serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9N, 9V, 14, 18C, 19A, 19F, 23F, 2, 8, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F). Because the polyclonal antibodies...

...10 serotypes (2, 8, 10A, 11A, 12F, 15B, 17F, 20, 22F and 33F) had limited serotype specificity, we replaced them with monoclonal antibodies for the 10 serotypes. To extend the serotype coverage beyond the 24 serotypes, we have adapted multiplexed PCR for five additional serotypes (15A, 15C, 16F, 35B and 38) to be useful with the pneumococcal lysates prepared for the multibead assay. We then validated the combined assay with 157 clinical...

...is robust and could be used to rapidly identify the serotypes of the majority of pneumococci (similar to 90%). In addition, the assay validation study suggests the presence of serological subtypes within serotype 11A.
...Identifiers--STREPTOCOCCUS-PNEUMONIAE SEROTYPES; MULTIPLEX PCR; CAPSULAR POLYSACCHARIDES; CONJUGATE VACCINE; ASSAY; IDENTIFICATION; IMMUNOASSAY; SEROGROUPS; DISEASE; LATEX

14/3,K/7 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

14861388 Genuine Article#: 012MV No. References: 28
Title: Validation of a multiplex pneumococcal serotyping assay with clinical samples
Author(s): Lin JS; Kaltoft MS; Brandao AP; Echaniz-Aviles G; Brandileone MCC; Hollingshead SK; Benjamin WH; Nahm MH (REPRINT)
Corporate Source: Univ Alabama,Dept Pathol,845 19th St S,BBRB 614/Birmingham//AL/35249 (REPRINT); Univ Alabama,Dept Pathol,Birmingham//AL/35249; Statens Serum Inst,WHO, Collaborating Ctr Reference & Res Pneumococci,Copenhagen//Denmark/; Adolfo Lutz Inst,Bacterial Sect,Sao Paulo//Brazil/; Fiocruz MS,IOC,BR-21045900 Rio De Janeiro//Brazil/; Natl Publ Hlth Inst,Dept Clin Epidemiol,Cuernavaca/Morelos/Mexico/; Univ Alabama,Dept Microbiol,Birmingham//AL/35294(nahm@uab.edu)
Journal: JOURNAL OF CLINICAL MICROBIOLOGY, 2006, V44, N2 (FEB), P383-388
ISSN: 0095-1137 Publication date: 20060200
Publisher: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Title: Validation of a multiplex pneumococcal serotyping assay with clinical samples
Abstract: We have recently developed a rapid pneumococcal serotyping method called "multibead assay" (J. Yu et al., J. Clin. Microbiol. 43:156-162, 2005) based on a multiplexed immunoassay for capsular polysaccharides in lysates of pneumococcal cultures. The multibead assay can identify 36 serotypes (1, 2, 3, 4 , 5, 6A, 6B, 7A/7F, 8, 9L/9N, 9V, 10A/10B/39/33C, 11A/11D/11F, 12A/12B/12F, 14, 15B/5C, 17F, 18C, 19A, 19F, 20, 22A/22F, 23F, and 33A/33F). More than 90% of the U.S. isolates express one of these...

...148:1136-1159, 1983). To validate the new assay, we examined 495 clinical isolates of pneumococci obtained in Brazil, Denmark, and Mexico. Pneumococci were serotyped by the Neufeld test in their countries of origin, and lysates of each...

...were noted, but 46 were due to nonreproducible technical problems or insufficient growth of the pneumococci. All of the isolates grew well for a second test, and therefore, the culture medium used for the multibead assay is adequate. The discrepancies persisted for eight isolates, involving the 6A, 11A, and 18C serotypes. Additional studies of the eight isolates showed that the discrepancies were due to differences...
...multibead or Neufeld tests for these three serotypes. For instance, five isolates were typed as 6A with the Neufeld test but as nontypeable by the multibead assay. Selection of another new monoclonal antibody (Hyp6AG1) for the multibead assay resulted in all five discrepant isolates typing as 6A. This finding indicates the validity of the multibead assay and emphasizes the need to validate any new pneumococcal serotyping assay with a large number of clinical isolates from different locations. It also suggests the presence of serological subtypes among isolates expressing the 6A serotype.
...Identifiers--STREPTOCOCCUS-PNEUMONIAE SEROTYPES; CONJUGATE VACCINE; PCR; LATEX; IMMUNOASSAY; RESISTANCE; SEROGROUPS; SPECIMENS

14/3,K/8 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

13498192 Genuine Article#: 888NB No. References: 26
Title: Rapid multiplex assay for serotyping pneumococci with monoclonal and polyclonal antibodies
Author(s): Yu JG; Lin JS; Benjamin WH; Waites KB; Lee CH; Nahm MH (REPRINT)
Corporate Source: 845 19th St S,BBRB 614/Birmingham//AL/35249 (REPRINT); Univ Alabama,Dept Pathol,Birmingham//AL/35294; Univ Alabama,Dept Microbiol,Birmingham//AL/35294; US FDA,Bethesda//MD/20014(Nahm@uab.edu)
Journal: JOURNAL OF CLINICAL MICROBIOLOGY, 2005, V43, N1 (JAN), P156-162
ISSN: 0095-1137 Publication date: 20050100
Publisher: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904 USA
Language: English Document Type: ARTICLE (ABSTRACT AVAILABLE)

Title: Rapid multiplex assay for serotyping pneumococci with monoclonal and polyclonal antibodies
Abstract: We have developed and characterized a rapid semiautomated pneumococcal serotyping system incorporating a pneumococcal lysate preparation protocol and a multiplex serotyping assay. The lysate preparation incorporates a bile solubility test to confirm pneumococcal identification that also enhances assay specificity. The multiplex serotyping assay consists of 24 assays specific for 36 serotypes: serotypes 1, 2, 3, 4, 5, 6A, 6B, 7A/7F, 8, 9L/9N, 9V, 10A/10B/39/(33C), 11A/11D/11F, 12A/12B/12F, 14, 15B/(15C), 17F, 18C, 19A, 19F, 20, 22A/22F, 23F, and 33A/33F. The multiplex assay requires a How cytometer, two sets of latex particles coated with pneumococcal polysaccharides, and serotype-specific antibodies. Fourteen newly developed monoclonal antibodies specific for common serotypes and a pool of...

...some of the less-common serotypes are used. The two monoclonal antibodies specific for serotypes 18C and 23F recognize serotype-specific epitopes that have not been previously described. These monoclonal antibodies make the identification of the 14 common serotypes invariant. The specificity of the serotyping assay is fully characterized with pneumococci of all known (i.e.,

90) serotypes. The assay is sensitive enough to use bacterial lysates diluted 20 fold. Our serotyping system can identify not only all the serotypes in pneumococcal vaccines but also most (>90%) of clinical isolates. This system should be very useful in serotyping clinical isolates for evaluating pneumococcal vaccine efficacy.
...Identifiers--STREPTOCOCCUS-PNEUMONIAE; CONJUGATE VACCINE; LATEX; 6B; IMMUNOASSAY; PCR

14/3,K/9 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

02060419 Genuine Article#: JX339 No. References: 31
Title: CAPSULAR TYPES OF STREPTOCOCCUS-PNEUMONIAE ISOLATED FROM BLOOD AND CSF DURING 1982-1987
Author(s): NIELSEN SV; HENRICHSEN J
Corporate Source: STATENS SERUM INST,WHO,COLLABORAT CTR REFERENCE& RES PNEUMOCOCCI,ARTILLERIVEJ 5/DK-2300 COPENHAGEN//DENMARK/; STATENS SERUM INST,WHO,COLLABORAT CTR REFERENCE& RES PNEUMOCOCCI,ARTILLERIVEJ 5/DK-2300 COPENHAGEN//DENMARK/
Journal: CLINICAL INFECTIOUS DISEASES, 1992, V15, N5 (NOV), P794-798
ISSN: 1058-4838
Language: ENGLISH Document Type: ARTICLE (Abstract Available)

Title: CAPSULAR TYPES OF STREPTOCOCCUS-PNEUMONIAE ISOLATED FROM BLOOD AND CSF DURING 1982-1987
Abstract: Knowledge about the type distribution of Streptococcus pneumoniae is fundamental to ensure an effective formulation of pneumococcal vaccine, especially with the possibility of producing a polysaccharide-protein-conjugated vaccine for the prevention of invasive disease in children. During the 6-year period 1982-1987, we received and typed 10,298 isolates from patients with invasive pneumococcal disease: 7,812 (76%) from blood and 2,486 (24%) from CSF. Of all isolates...

...recovered from individuals in Europe and 23% were from children. In order of frequency, S. pneumoniae types 6A + 6B, 14, 18C, 19F, 1, 7F, 23F, 19A, 4, and 5 were most commonly isolated from children, and types 3, 1, 14, 7F, 4, 6A + 6B, 8, 23F, 9V, and 19F, from adults. The pneumococcal types in the currently available 23-valent vaccine represented 87% of all isolates in this study, but the proportion of vaccine types varied somewhat with age and source. In all pneumococcal groups included in the vaccine, the vaccine types represented >80% of the isolates, except in...
...Identifiers--SEROTYPE DISTRIBUTION; PNEUMOCOCCAL DISEASE; CEREBROSPINAL-FLUID; INFECTIONS; EPIDEMIOLOGY; VACCINE; BACTEREMIA; RESISTANCE; CHILDREN; INFANTS
Research Fronts: 90-6123 001 (PNEUMOCOCCAL VACCINATION; CAPSULAR POLYSACCHARIDE; IGG RESPONSES; SYSTEMIC IMMUNIZATION; SPLENECTOMIZED CHILDREN; COMMUNITY-ACQUIRED PNEUMONIA)

14/3,K/10 (Item 1 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

0008071983 SUPPLIER NUMBER: 2009229144
Current knowledge regarding the investigational 13-valent pneumococcal conjugate vaccine
Dinleyici E.C.; Yargic Z.A.

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CORRESP. AUTHOR/AFFIL: Dinleyici E. C., Eskisehir Osmangazi University, Faculty of Medicine, Department of Pediatrics, Eskisehir, TR-26480, Turkey
CORRESP. AUTHOR EMAIL: timboothtr@yahoo.com
Journal: Expert Review of Vaccines (Expert Rev. Vaccines), v8, n8, (977-986), 2009, United Kingdom
PUBLICATION DATE: August 1, 2009 (20090801)
CODEN: ERVXA
ISSN: 1476-0584 eISSN: 1744-8395
PUBLISHER: Expert Reviews Ltd.
RECORD TYPE: Abstract; New
DOCUMENT TYPE: Review
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 61

Current knowledge regarding the investigational 13-valent pneumococcal conjugate vaccine

The introduction of a 7-valent pneumococcal conjugate vaccine (PCV-7) into the routine childhood vaccination schedule has been shown to be effective in preventing invasive pneumococcal disease (IPD), pneumonia, otitis media and meningitis in infants and young children as determined by epidemiological surveillance studies...

...overall reduction in IPD. Non-PCV-7 serotypes and vaccine-related serotypes, such as serotypes 1, 5, 7F, 6A and 19A, have also been reported to cause IPD in some parts of the world where morbidity and mortality from pneumococcal disease are higher. An investigational 13-valent pneumococcal conjugate vaccine (PCV-13) uses CRM197 as a carrier, similar to the current PCV-7, and covers serotypes 1, 3, 5, 6A, 7F and 19A, in addition to the serotypes of PCV-7 (serotype 4, 6B, 9V, 14, 18C, 19F and 23F). PCV-13 is safe and well tolerated with other pediatric vaccines in infants according to...

...PCV-7 and, according to immunogenicity studies, PCV-13 has more potential to protect against pneumococcal diseases with the additional six serotypes. With the addition of these new serotypes, it could be possible to cover potential pneumococcal serotypes causing IPD throughout the world. The cost of the vaccine, its length of duration ...

DESCRIPTORS:
13-valent pneumococcal conjugate vaccine...

...7-valent pneumococcal conjugate vaccine...

...Pneumococcal vaccine

14/3,K/11 (Item 1 from file: 72)
DIALOG(R)File 72:EMBASE

0080888089 EMBASE No: 2005533014
Determination of saccharide content in pneumococcal polysaccharides and conjugate vaccines by GC-MSD
Kim J.S.; Laskowich E.R.; Arumugham R.G.; Kaiser R.E.; MacMichael G.J.
Wyeth Vaccine, Research and Development, 4300 Oak Park, Sanford, NC 27330, United States
AUTHOR EMAIL: kimj9@wyeth.com
CORRESP. AUTHOR/AFFIL: Kim J.S.: Wyeth Vaccine, Research and Development,

4300 Oak Park, Sanford, NC 27330, United States
CORRESP. AUTHOR EMAIL: kimj9@wyeth.com

Analytical Biochemistry (Anal. Biochem.) (United States) December 15, 2005, 347/2 (262-274)
CODEN: ANBCA ISSN: 0003-2697 eISSN: 1096-0309
PUBLISHER ITEM IDENTIFIER: S0003269705006883
DOI: 10.1016/j.ab.2005.09.022
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 33

Determination of saccharide content in pneumococcal polysaccharides and conjugate vaccines by GC-MSD

A simple and sensitive gas chromatographic method was designed for quantitative analysis of Streptococcus pneumoniae capsular polysaccharides, activated polysaccharides, and polysaccharide conjugates. Pneumococcal serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F polysaccharide or conjugate were subjected to methanolysis in 3 N hydrochloric acid in methanol followed by re-N-acetylation and trimethylsilylation. Derivatized samples were...

...and chromatography procedure. Response factors generated from authentic monosaccharide standards were used for quantitation of pneumococcal polysaccharides and conjugates with confirmation of peak assignments by retention time and mass spectral analysis. This method allows saccharide quantitation in multivalent pneumococcal vaccine intermediates and final drug products with low-level detection (10 pg) and peak purity...

DRUG DESCRIPTORS:
*carbohydrate; *Pneumococcus vaccine--drug analysis--an
MEDICAL DESCRIPTORS:
article; colorimetry; methanolysis; priority journal; quantitative analysis ; serotype; standardization; Streptococcus pneumoniae

14/3,K/12 (Item 2 from file: 72)
DIALOG(R)File 72:EMBASE

0078753540 EMBASE No: 2001359897
Evolution of Streptococcus pneumoniae serotypes and penicillin susceptibility in Latin America, Sireva-Vigia Group, 1993 to 1999

Di Fabio J.L.; Castaneda E.; Agudelo C.I.; De La Hoz F.; Hortal M.; Camou T.; Echaniz-Aviles G.; Carnalla Barajas M.N.; Heitmann I.; Hormazabal J.C.; Brandileone M.C.C.; Dias Vieira V.S.; Regueira M.; Ruvinski R.; Corso A.; Lovgren M.; Talbot J.A.; De Quadros C.

Pediatric Infectious Disease Journal (Pediatr. Infect. Dis. J.) (United States) October 24, 2001, 20/10 (959-967)
CODEN: PIDJE ISSN: 0891-3668
DOI: 10.1097/00006454-200110000-00009
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 52

Evolution of Streptococcus pneumoniae serotypes and penicillin susceptibility in Latin America, Sireva-Vigia Group, 1993 to 1999

...Chile, Colombia, Mexico and Uruguay aimed at monitoring capsular types

and antimicrobial susceptibility of Streptococcus pneumoniae causing invasive disease in children <6 years of age. Methods. The surveillance system included children 6 years of age and younger with invasive disease caused by S. pneumoniae. The identification, capsular typing and susceptibility to penicillin of the isolates were conducted using a common protocol, based on standard methodologies. Results. By June, 1999, 4105 invasive pneumococcal isolates had been collected mainly from pneumonia (44.1%) and meningitis (41.1%) cases. Thirteen capsular types accounting for 86.1% of the isolates (14, 6A/6B, 5, 1, 23F, 19F, 18C, 19A, 9V, 7F, 3, 9N and 4) remained the most common types during the surveillance period. Diminished susceptibility to penicillin was detected in 28.6% of the isolates, 17.3% with intermediate and 11. 3% with high level resistance. Resistance varied among countries and increased during this period in Argentina, Colombia and Uruguay. Serotypes 14 and 23F accounted for 66.6% of the resistance. Conclusion. These surveillance data clearly demonstrate the potential impact of the introduction of a conjugate vaccine on pneumococcal disease and the need for more judicious use of antibiotics to slow or reverse the...

DRUG DESCRIPTORS:
antibiotic agent; Pneumococcus vaccine
MEDICAL DESCRIPTORS:
*antibiotic sensitivity; *Streptococcus pneumoniae
...Colombia; female; health survey; human; major clinical study; male; Mexico; nonhuman; preschool child; priority journal; serotype; Uruguay

14/3,K/13 (Item 3 from file: 72)
DIALOG(R)File 72:EMBASE

0078123488 EMBASE No: 2000172776
A latex bead-based flow cytometric immunoassay capable of simultaneous typing of multiple pneumococcal serotypes (multibead assay)
Park M.K.; Briles D.E.; Nahm M.H.
Department of Pediatrics, University of Rochester, Rochester, New York 14642, United States
AUTHOR EMAIL: moon@vaccine.rochester.edu
CORRESP. AUTHOR/AFFIL: Nahm M.H.: University of Rochester, Department of Pediatrics, Box 777, 601 Elmwood Ave., Rochester, NY 14642, United States
CORRESP. AUTHOR EMAIL: moon@vaccine.rochester.edu

Clinical and Diagnostic Laboratory Immunology (Clin. Diagn. Lab. Immunol.) (United States) May 1, 2000, 7/3 (486-489)
CODEN: CDIME ISSN: 1071-412X
DOI: 10.1128/CDLI.7.3.486-489.2000
DOCUMENT TYPE: Journal; Article RECORD TYPE: Abstract
LANGUAGE: English SUMMARY LANGUAGE: English
NUMBER OF REFERENCES: 14

A latex bead-based flow cytometric immunoassay capable of simultaneous typing of multiple pneumococcal serotypes (multibead assay)

A simple and rapid method of simultaneously determining 15 Streptococcus pneumoniae serotypes was developed. Fifteen latex beads of different sizes and different red fluorescence levels were coated with 1 of 15 serotypes (1, 3, 4, 5, 6A, 6B, 7F , 9N, 9V, 14, 18C, 19A, 19F, 22F, and 23F) of pneumococcal capsular polysaccharide (PS). The bead mixture was incubated with individual pneumococcal lysate, a pool of rabbit antisera capable of binding the 15 serotypes, and fluorescein (green

fluorescence)-conjugated anti-rabbit antibody. Bead size, red fluorescence, and green fluorescence were measured in a single...

...when there was a serotypic match between PS on the bead and PS in the pneumococcal lysate. This method distinguished cross-reactive serotypes and correctly identified the serotypes in 100% of 86 pneumococcal isolates tested.

DRUG DESCRIPTORS:
*latex; *Pneumococcus vaccine
MEDICAL DESCRIPTORS:
article; bacterium isolate; cell lysate; controlled study; flow cytometry; fluorescence; immunoassay; nonhuman; priority journal; serotype; Streptococcus pneumoniae

14/3,K/14 (Item 1 from file: 162)
DIALOG(R)File 162:Global Health

0005399963 CAB Accession Number: 20083265124
Use of silica desiccant packets for specimen storage and transport to evaluate pneumococcal nasopharyngeal carriage among Nepalese children.
Joshi, H. H.; Gertz, R. E., Jr.; Carvalho, M. da G.; Beall, B. W.
Author email address: bbeall@cdc.gov
Respiratory Diseases Branch, Division of Bacterial Diseases, Centers for Disease Control and Prevention, Atlanta, GA 30333, USA.
Journal of Clinical Microbiology vol. 46 (9): p.3175-3176
Publication Year: 2008
ISSN: 0095-1137
Digital Object Identifier: 10.1128/JCM.00906-08
Publisher: American Society for Microbiology (ASM) Washington, USA
Language: English
Record Type: Abstract
Document Type: Correspondence

Use of silica desiccant packets for specimen storage and transport to evaluate pneumococcal nasopharyngeal carriage among Nepalese children.
Silica desiccant packages (SDPs) containing 1.5 g of silica powder were tested for storage and transport of nasopharyngeal (NP) specimens. NP swabs were collected from 302 healthy children aged 1-15 years at a children's homeless shelter in Ranibari, Kathmandu, Nepal. The samples were...

... maximal storage duration of 25 days. The NP samples were then cultured and examined for pneumococci. Of the 302 NP samples, 184 (61%) were positive for pneumococci . The level of carriage was high (69-83%) within the 1-2, 3-4, 5-6 and 7-8 years age groups and incrementally decreased among older ages. The carriage among children aged 1-10 years was 71% (156 of 221). There was no difference in pneumococcal recovery between NP specimens processed after 12 and 25 days. Of the 184 pneumococci-positive samples, 160 were serotypeable (43 serotypes), with one mixed-carriage isolate detected. All isolates were susceptible to penicillin. Four of 9 conventionally serotyped 6A isolates were subsequently typed as newly discovered serotype 6C but were identified in the present study as serotype 6A . 37 (23%) of 160 isolates were covered by the 7-valent conjugate vaccine (vaccine serotypes 4, 6B, 9V, 14, 18C, 19F, 23F and 6A), and 52 of 160 (32%) were covered by a 13-valent vaccine (vaccine serotypes 1, 3, 5, 6A, 7F and 19A) in development. It is

concluded that the level of pneumococcal carriage among Nepalese children is high. NP swabs can be maintained in SDPs in room...

...ORGANISM DESCRIPTORS: Streptococcus pneumoniae

14/3,K/15 (Item 1 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports

0000211427 (USE FORMAT 7 OR 9 FOR FULLTEXT)
Researchers' work adds to pneumococcal vaccines body of knowledge
Immunotherapy Weekly, May 4, 2005, p.69

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
WORD COUNT: 1152

Researchers' work adds to pneumococcal vaccines body of knowledge

TEXT: Pneumococcal vaccines data are the focus of recent research from the United States and The Netherlands.

Study 1: Scientists have developed a rapid multiplex assay for serotyping pneumococci with monoclonal and polyclonal antibodies.

... a study from the United States, "We have developed and characterized a rapid semi-automated pneumococcal serotyping system incorporating a pneumococcal lysate preparation protocol and a multiplex serotyping assay. The lysate preparation incorporates a bile solubility test to confirm pneumococcal identification that also enhances assay specificity. The multiplex serotyping assay consists of 24 assays specific for 36 serotypes: serotypes 1, 2, 3, 4, 5, 6A, 6B, 7A/7F, 8, 9L/9N, 9V, 10A/10B/39/(33C), 11A/11D/11F, 12A/12B/12F, 14, 15B/(15C), 17F, 18C, 19A, 19F, 20, 22A/22F, 23F, and 33A/33F."

"The multiplex assay requires a How cytometer, two sets of latex particles coated with pneumococcal polysaccharides, and serotype-specific antibodies," said Jigui Yu and colleagues at the University of Alabama-Birmingham and the...

...some of the less-common serotypes are used. The two monoclonal antibodies specific for serotypes 18C and 23F recognize serotype-specific epitopes that have not been previously described. These monoclonal antibodies make the identification of the 14 common serotypes invariant."

"The specificity of the serotyping assay is fully characterized with pneumococci of all known (i.e., 90) serotypes," stated the researchers. "The assay is sensitive enough...

...lysates diluted 20-fold. Our serotyping system can identify not only all the serotypes in pneumococcal vaccines but also most (>90%) of clinical isolates. This system should be very useful in serotyping clinical isolates for evaluating pneumococcal vaccine efficacy."

Yu and associates published their study in the Journal of Clinical Microbiology (Rapid multiplex assay for serotyping pneumococci with monoclonal and polyclonal antibodies. J Clin Microbiol, 2005;43(1):156-162).

For more information, contact Moon H. Nahm, 845 19th Street South, BBRB 614...

...Study 2: The multiplex opsonophagocytosis assay is a useful tool for monitoring the 7-valent pneumococcal conjugate vaccine.

"Pneumococcal conjugate vaccination is highly efficacious against invasive diseases in young children. Since host protection is

mainly...

...throughput method, which simultaneously measures the opsonophagocytosis against the seven serotypes covered by the current conjugate vaccine in a single assay," scientists writing in the journal Vaccine report.
"In the so...

...assay (MOPA), a mixture containing equal numbers of colony forming units (CFUs) of chloramphenicol-resistant serotype 4, spectinomycin-resistant serotype 613, streptomycin-resistant serotype 9V, erythromycin-resistant serotype 14, rifampicin-resistant serotype 18C, tetracycline-resistant serotype 19F, and trimethoprim-resistant serotype 23F pneumococci was used as a target mixture and incubated with serial dilutions of test serum," said...

...simultaneously measures opsonophagocytosis capacity of serum against the capsular serotypes included in the 7-valent pneumococcal conjugate vaccine in a high-throughput fashion, requiring low volumes of patient sera."
Bogaert and associates...

...Vaccine (Multiplex opsonophagocytosis assay (MOPA): a useful tool for the monitoring of the 7-valent pneumococcal conjugate vaccine. Vaccine, 2004;22(29-30):4014-4020).
Additional information can be obtained by contacting...

...Box 1738, NL-3000 DR Rotterdam, The Netherlands. E-mail: p.hermans@erasmusmc.nl.
Study 3: Investigators have studied the base hydrolysis of phosphodiester bonds in pneumococcal polysaccharides.
According to recent research published in the journal Biopolymers , "A comprehensive study of the base hydrolysis of all phosphodiester bond-containing capsular polysaccharides of the 23-valent pneumococcal vaccine is described here. Capsular polysaccharides from serotypes 6B, 10A, 17F, 19A, 19F, and 20 contain a phosphodiester bond that connects the repeating units in these polysaccharides (also referred to as backbone phosphodiester bonds), and polysaccharides from serotypes 11A, 15B, 18C, and 23F contain a phosphodiester bond that links a side chain to their repeating units."
"Molecular weight...

...researchers found, "the relative order of backbone phosphodiester bond instability due to base hydrolysis was 19A > 10A > 19F > 6B > 17F, 20. Degradation of side-chain phosphodiester bonds was not observed, although the high, degree...

...the side chains to the total polysaccharide molecular weight. In comparison with literature data on pneumococcal polysaccharide 6A, 19A was found to be the more labile, and hence appears to be the most labile pneumococcal polysaccharide studied to date. The rate of hydrolysis increased at higher pH and in the...

...conditions."
Pujar and associates published their study in Biopolymers (Base hydrolysis of phosphodiester bonds in pneumococcal polysaccharides. Biopolymers, 2004;75(1):71-84).
For additional information, contact Narahari S. Pujar, Merck & Company Inc., Merck Research Laboratories, WP17-301, PO Box 4, West Point, PA 19486, USA. E-mail: hari...

...pujar@merck.com.
The information in this article comes under the major subject areas of

Pneumococcal Vaccine, Pneumococcal Polysaccharide,
Pneumococcus, Bacteriology, Vaccine Development, and Proteomics.
     This article was prepared by Immunotherapy Weekly editors from staff
...

DESCRIPTORS: Antimicrobial Resistance; Bacteriology; Drug Development
              ; Merck; Pharmaceuticals; Pneumococcal
              Polysaccharide; Pneumococcal Vaccine;
              Pneumococcal Vaccines; Pneumococcus; U.S.
              Food & Drug Administration; Vaccine Development; and
              Proteomics; All News; Professional
SUBJECT HEADING: Pneumococcal Vaccines

 14/3,K/16   (Item 2 from file: 135)
DIALOG(R)File 135:NewsRx Weekly Reports

0000199549   (USE FORMAT 7 OR 9 FOR FULLTEXT)
Researchers detail new studies and findings in the area of
pneumococcal vaccines
Biotech Business Week, March 14, 2005, p.378

DOCUMENT TYPE: Expanded Reporting LANGUAGE: English
RECORD TYPE: FULLTEXT
WORD COUNT: 1185

Researchers detail new studies and findings in the area of
pneumococcal vaccines

TEXT: Pneumococcal vaccines data are the focus of recent research
from the United States and South Korea.
     Study 1: Scientists have assigned weight-based antibody units
for 13 serotypes to a human antipneumococcal standard...
...   antipneumococcal standard reference serum lot 89-S, also known as
lot 89-SF, for Streptococcus pneumoniae capsular polysaccharide
(PnPs) serotypes 2, 6A, 8, 9N, 10A, 11A, 12F, 1513, 19A, 17F,
20, 22F, and 33F, as well as for C-polysaccharide (C-Ps), extending the
standard's usefulness for pneumococcal vaccine evaluation beyond the
original serotype 1, 3, 4, 5, 611, 7F,
9V, 14, 18C, 19F, and 23F assignments. The
additional 14 assignments were determined using an equivalence of
absorbance method with an anti-PnPs serotype 613 reference
enzyme-linked immunosorbent assay (EIA)."
     "To assure accuracy, anti-PnPs EIA for serotype 14
antibodies, a previously assigned serotype, was performed
concurrently," said Sally A. Quataert and collaborators at Wyeth Vaccines
Research and the...

...in lot 89-S agrees well with the separately determined total Ig
assignment for each serotype. The lot 89-S assignments for serotypes
1, 5, 613, 14, 18C, 19F, and 23F were used
for pneumococcal conjugate vaccine clinical trial evaluation
and to generate data in efficacy trials where serological correlates for
protection have been proposed."
     "The assignment of antibody concentrations to additional
pneumococcal serotypes in this reference reagent facilitates the
consistent and accurate comparison of serum antibody concentrations...

...NY 10965, USA. E-mail: hubt@wyeth.com.
     Study 2: The ClpP protease of Streptococcus pneumoniae modulates
virulence expression and protects against fatal pneumococcal
challenge.

According to recent research from South Korea and Australia, " Streptococcus pneumoniae usually colonizes the nasopharynx of humans asymptomatically but occasionally translocates from this niche to the...

...and the expression of virulence factors, such as capsular polysaccharide, and virulence proteins, such as pneumolysin (Ply), PspA, and CbpA. Modulation of the expression of pneumococcal virulence genes by heat shock and by heat shock proteins ClpL and ClpP, as well...

...The half-lives of the mRNAs of ply and of the first gene of the serotype 2 capsule synthesis locus [cps(2)A] in the clpP mutant were more than two...

...of mice with ClpP elicited a protective immune response against fatal systemic challenge with S. pneumoniae D39, making ClpP a potential vaccine candidate for pneumococcal disease."

Kwon and associates published their study in Infection and Immunity (The ClpP protease of Streptococcus pneumoniae modulates virulence expression and protects against fatal pneumococcal challenge. Infec Immunity, 2004;72(10):5646-5653).

For additional information, contact Dong-Kwon Rhee...

...of Pharmacy, Sungkyunkwan University, Suwon 440-746, South Korea. E-mail: dkrhee@skku.edu.

Study 3: Investigators have studied the base hydrolysis of phosphodiester bonds in pneumococcal polysaccharides.

According to recent research published in the journal Biopolymers , "A comprehensive study of the base hydrolysis of all phosphodiester bond-containing capsular polysaccharides of the 23-valent pneumococcal vaccine is described here. Capsular polysaccharides from serotypes 6B, 10A, 17F, 19A, 19F, and 20 contain a phosphodiester bond that connects the repeating units in these polysaccharides (also referred to as backbone phosphodiester bonds), and polysaccharides from serotypes 11A, 15B, 18C, and 23F contain a phosphodiester bond that links a side chain to their repeating units."

"Molecular weight...

...researchers found, "the relative order of backbone phosphodiester bond instability due to base hydrolysis was 19A > 10A > 19F > 6B > 17F, 20. Degradation of side-chain phosphodiester bonds was not observed, although the high, degree...

...the side chains to the total polysaccharide molecular weight. In comparison with literature data on pneumococcal polysaccharide 6A, 19A was found to be the more labile, and hence appears to be the most labile pneumococcal polysaccharide studied to date. The rate of hydrolysis increased at higher pH and in the...

...conditions."

Pujar and associates published their study in Biopolymers (Base hydrolysis of phosphodiester bonds in pneumococcal polysaccharides. Biopolymers, 2004;75(1):71-84).

For additional information, contact Narahari S. Pujar, Merck & Company Inc., Merck Research Laboratories, WP17-301, PO Box 4, West Point, PA 19486, USA. E-mail: hari...

...pujar@merck.com.

The information in this article comes under the major subject areas of Pneumococcal Vaccine, Pneumococcal Polysaccharide, Pneumococcus, Bacteriology, Vaccine Development, and Proteomics.

This article was prepared by Biotech Business Week editors from...

SUBJECT HEADING: Pneumococcal Vaccines

14/3,K/17 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0462655 DBR Accession No.: 2009-08096 PATENT
Immunogenic composition for immunizing human host against Neisseria meningitidis infection, has at least two different N.meningitidis capsular saccharide or different saccharide conjugated separately to same type of carrier protein - pharmaceutical composition comprising Neisseria meningitidis capsular saccharide, useful as vaccine for treatment and prevention of Neisseria meningitidis infection
AUTHOR: BIEMANS R L; BOUTRIAU D; CAPIAU C; DENOEL P; DUVIVIER P; POOLMAN J
PATENT ASSIGNEE: GLAXOSMITHKLINE BIOLOGICALS SA 2007
PATENT NUMBER: WO 200700341 PATENT DATE: 20070104 WPI ACCESSION NO.: 2009-K39787 (200940)
PRIORITY APPLIC. NO.: GB 200526041 APPLIC. DATE: 20051221
NATIONAL APPLIC. NO.: WO 2006EP6268 APPLIC. DATE: 20060623
LANGUAGE: English

...Neisseria meningitidis infection, has at least two different N.meningitidis capsular saccharide or different saccharide conjugated separately to same type of carrier protein - pharmaceutical composition comprising Neisseria meningitidis capsular saccharide, useful...
...ABSTRACT: An immunogenic composition comprising at least two different Neisseria meningitidis capsular saccharides or different saccharides conjugated separately to same type of carrier protein, where one or more saccharides is/are chosen from first group with MenA, MenC, MenY and MenW that is/are conjugated to protein carriers, where saccharide:protein ratio (w/w) is 1:2-1:5 and different saccharides is/are chosen from second group with MenA, MenC, MenY and MenW that is/are conjugated to a protein carriers having saccharide:protein ratio (w/w) of 5:1-1:1.99, is new. DETAILED DESCRIPTION - An immunogenic composition comprises at least two different Neisseria meningitidis capsular saccharides or different saccharides conjugated separately to the same type of carrier protein, where one or more of the saccharides...

...are chosen from first group consisting of MenA, MenC, MenY and MenW that is/are conjugated to a protein carriers, where the saccharide:protein ratio (w/w) is 1:2-1:5, and one or more different saccharides is/are chosen from a second group consisting of MenA, MenC, MenY and MenW that is/are conjugated to a protein carriers having the saccharide:protein ratio (w/w) of 5:1-1:1.99. INDEPENDENT CLAIMS are also included for: (1) a vaccine comprising the immunogenic composition and an excipient; (2) a vaccine kit for concomitant...

...and whole-cell or acellular pertussis components, and a second container comprising the immunogenic composition; (3) producing the vaccine, involves mixing the immunogenic composition with an excipient; (4) immunizing a human host against disease caused by N.meningitidis infection, involves administering to the host an immunoprotective dose of the immunogenic composition or vaccine; and (5) use of the immunogenic composition in the manufacture of a medicament for treating or preventing...

...or more of the saccharides is/are chosen from MenA and MenC that is/are conjugated to a protein carriers, where the saccharide:protein ratio (w/w) is 1:2-1:5 and one or more different

saccharides is/are chosen from MenC, MenY and MenW that is/are conjugated to a protein carriers, where the saccharide:protein ratio (w/w) is 5:1-1:1.99. The MenW is present and the ratio of MenW saccharide to carrier protein is 5:1-1:1.99, 2:1-1:1.99, 1.5:1-1:1.8, 1:1-1:1.7, 1:1.2-1:1.6 or 1:1.4-1:1.5 (w/w). The MenY is present and the ratio of MenY saccharide to carrier protein is 5:1-1:1.99, 2:1-1:1.99, 1.5:1-1:1.9, 1:1-1:1.8, 1:1.1-1:1.6 or 1:1.3-1:1.4 (w/w). The MenA is present and the ratio of MenA saccharide to carrier protein is 1:2-1:5, 1:2.4-1:4, 1:2.7-1:3.5 or 1:2.9-1:3.1 (w/w). The MenC is present and the ratio of MenC saccharide to carrier protein is 5:1-1:1.99, 2:1-1:1.99, 1.5:1-1:1.8, 1.3:1-1:1.6, 1.2:1-1:1.4 or 1.1:1-1:1.2 (w/w); or 1:2-1:5, 1:2.5-1:4.5, 1:2.7-1:4.3, 1:3-1:4 or 1:3.3-1:3.5 (w/w). One or more N.meningitidis capsular saccharides is/are chosen from MenA, MenC, MenY and MenW that are conjugated through a linker to the carrier proteins, and one or more different saccharides is/are chosen from MenA, MenC, MenY and MenW that is/are directly conjugated to a carrier proteins. One or more N.meningitidis capsular saccharides is/are chosen from MenA and MenC that is/are conjugated through a linker to a carrier proteins, and one or more different saccharides is/are chosen from MenC, MenY and MenW that is/are directly conjugated to a carrier proteins. The composition comprises MenA capsular saccharide conjugated through linker to carrier protein, and MenC capsular saccharide directly conjugated to carrier protein. The composition comprises MenC capsular saccharide conjugated through linker to carrier protein and MenY capsular saccharide directly conjugated to carrier protein. The MenA and MenC capsular saccharides conjugated through linker to carrier proteins and MenY and Men W capsular saccharides directly conjugated to carrier proteins. The MenA capsular saccharide conjugated through linker to carrier protein, and MenC, MenY and MenW capsular saccharides directly conjugated to carrier proteins. Each N.meningitidis capsular saccharide is conjugated to carrier protein independently chosen from TT, DT, CRM197, fragment C of TT and protein D. Each N.meningitidis capsular saccharide is conjugated to the same carrier protein chosen from TT, DT, CRM197, fragment C of TT and protein D, preferably TT. Each N.meningitidis capsular saccharide is separately conjugated to separate carrier protein. At least one, two or three N.meningitidis capsular saccharide conjugates is directly conjugated to carrier protein. The MenW and/or MenY, MenW and/or MenC, MenY and/or MenC, or MenW, MenC and MenY are directly conjugated to carrier protein. At least one, two or three N.meningitidis saccharide conjugates is directly conjugated by CDAP chemistry. At least one, two or three N.meningitidis capsular saccharides are conjugated to the carrier protein through a linker. The linker is bifunctional. The linker has two...

... one end and a reactive carboxylic acid group at the other end. The linker has 4 -12 carbon atoms, where the linker is ADH. Each N.meningitidis capsular saccharides conjugated through a linker are conjugated to the linker with CDAP chemistry. The carrier protein is conjugated to the linker using carbodiimide chemistry, optionally using EDAC. Each N.meningitidis capsular saccharide is

conjugated to the linker before the carrier protein is conjugated to the linker. The MenA or MenC is conjugated to a carrier protein through linker. The N.meningitidis capsular saccharides from at least two of serogroups A, C, W135 and Y conjugated to a carrier protein to produce N.meningitidis capsular saccharide conjugate , where the average size of each N.meningitidis saccharide is above 5O kDa, 75 kDa...

...sized by microfluidization. Each N.meningitidis capsular saccharide is a native polysaccharide. The N.meningitidis conjugates are made from a mixture of some native polysaccharides and other saccharides that are sized...

...140-180 kDa, 150-170 kDa or 110-140 kDa. The dose of each saccharide conjugate is 2-20 micrograms, 3-10 micrograms, 4-7 micrograms or around (or exactly) 5 micrograms of saccharide. The composition further comprises H.influenzae b capsular saccharide (Hib) conjugated to a carrier protein. The H.influenzae b capsular saccharide is conjugated to a carrier protein chosen from TT, DT, CRM197, fragment C of TT and protein D, preferably TT. The Hib saccharide is conjugated to the same carrier protein as for at least one, two, three or all of the N.meningitidis capsular saccharide conjugates . The ratio of Hib to carrier protein in the Hib capsular saccharide conjugate is of 1:5-5: 1 (w/w), or 1:1-1:4, 1:2-1: 3.5 or around 1:3 (w/w). The Hib capsular saccharide is conjugated to the carrier protein through a linker. The Hib saccharide is conjugated to the carrier protein or linker using CNBr or CDAP. The carrier protein is conjugated to the Hib saccharide through the linker using carbodiimide chemistry, optionally EDAC chemistry. The composition comprises Hib saccharide conjugate and at least two further bacterial saccharide conjugates, where the Hib conjugate is present in a lower dose than the mean dose of the at least two further bacterial saccharide conjugates. The Hib conjugate is present in a lower dose than the dose of each of the at least two further bacterial saccharide conjugates. At least two further bacterial saccharide conjugates comprises N.meningitidis serogroup C capsular saccharide (MenC) conjugate , serogroup Y capsular saccharide (MenY) conjugate, serogroup A capsular saccharide (MenA) conjugate, or serogroup W135 capsular saccharide (MenW) conjugate. At least two further bacterial saccharide conjugates comprise Streptococcus pneumoniae capsular saccharide derived from a strain chosen from serotypes 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F. At least two bacterial saccharide conjugates comprise a Salmonella typhi Vi capsular saccharide. The dose of the Hib saccharide conjugate is of 0.1-9 micrograms, 1-5 micrograms or 2-3 micrograms of saccharide. The dose of each of the at least two further saccharide conjugates is of 2-20 micrograms, 3-10 micrograms, 4 -7 micrograms, or around or exactly 5 micrograms of saccharide. The saccharide dose of the Hib saccharide conjugate is less than 90%, 75% or 60%, between 20% and 60%, or around 50% of the mean saccharide dose of the at least two further saccharide conjugates . The same carrier protein is used in the Hib conjugate and two or more of the at least two further bacterial saccharide conjugates. The composition comprises N.meningitidis serogroup B outer membrane vesicle preparation or capsular saccharide. One or more saccharides is/are conjugated to the carrier protein through a first type of chemical group on the protein carrier, and one or more saccharides is/are conjugated to the carrier protein through a

second type of chemical group on the protein carrier. One or more saccharides conjugated to the carrier protein through the first type of chemical group on the protein carrier, are different to the one or more saccharides conjugated to the carrier protein through the second type of chemical group on the protein carrier. One or more saccharides is/are conjugated to the carrier protein through a carboxyl group on the protein carrier, and one or more saccharides is/are conjugated to the carrier protein through an amino group on the protein carrier. The first and...

... Streptococcus group IV capsular saccharide, Group B Streptococcus group V capsular saccharide, Staphylococcus aureus type 5 capsular saccharide, Staphylococcus aureus type 8 capsular saccharide, Vi saccharide from Salmonella typhi, N.meningitidis...
...and/or L2), Moraxella catarrhalis LPS, H.influenzae LPS, and from any of the capsular pneumococcal saccharides such as from serotype : 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F or 33F. The composition comprises at least 2 different N.meningitidis capsular saccharides, where one or more of the saccharides is/are chosen from MenA and MenC that is/are conjugated to the carrier protein through the first type of chemical group on the protein carrier...

... is/are chosen from second group consisting of MenC, MenY and MenW that is/are conjugated to the carrier protein through the second type of chemical group on the protein carrier...

... of chemical group is an amino group on the protein carrier. The composition comprises MenA conjugated through the first type of chemical group and MenC conjugated through the second type of chemical group; MenC conjugated the first type of chemical group and MenY conjugated through the second type of chemical group; MenA conjugated through the first type of chemical group and MenC, MenY and MenW conjugated through the second type of chemical group; or MenA and MenC conjugated through the first type of chemical group, and MenY and MenW conjugated through the second type of chemical group. The Hib is conjugated to the same type of carrier protein as the N.meningitidis saccharides. The Hib is conjugated to the carrier protein through either the first or second type of chemical group. One or more saccharides (e.g. MenA and/or MenC) conjugated to the carrier protein with a saccharide:protein ratio (w/w) of 1:2-1:5 are conjugated through a linker. Each capsular saccharides conjugated through a linker is conjugated to the linker with CDAP chemistry. Each capsular saccharide is conjugated to the linker before the carrier protein is conjugated to the linker, or the linker is conjugated to the saccharide before it is conjugated to the carrier protein. One or more saccharides (e.g. MenY, MenW and/or MenC) conjugated to the carrier protein with a saccharide:protein ratio (w/w) of 5:1-1: 1.99 are directly conjugated. ACTIVITY - Antibacterial. MECHANISM OF ACTION - Vaccine. Analysis of Neisseria meningitidis capsular saccharides e.g. MenC...

... N.meningitidis infection was carried out as follows. A subject was administered with Hib-MenCY (5 micrograms) and Infanrix (RTM: Not defined) penta, Hib-MenC (~5 mg) and Infanrix (RTM: Not defined) penta, and Menjugate (RTM: Not defined) and Infanrix (RTM...

... of the antibody against N.meningitidis serogroups C and Y antigen (MenC and Y polysaccharide conjugates) was found to be 100% and 99.6% respectively. Results showed that the MenC and Y polysaccharide

conjugates produced an excellent immune response in the treated subject, compared to control. USE - For immunizing...

14/3,K/18 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0440576 DBR Accession No.: 2007-27434 PATENT
Making immunogenic conjugate comprising Streptococcus pneumoniae serotype 3 polysaccharide useful for treating pneumococcal infection, involves periodic acid oxidation of hydrolyzed serotype 3 polysaccharide in presence of bivalent cations - preparation of vaccine comprising polysaccharide-protein conjugate for preventing Streptococcus pneumoniae infection
AUTHOR: HAUSDORFF W P; SIBER G R; PARADISO P R; PRASAD A K
PATENT ASSIGNEE: WYETH 2007
PATENT NUMBER: US 20070231340 PATENT DATE: 20071004 WPI ACCESSION NO.: 2007-751332 (200770)
PRIORITY APPLIC. NO.: US 644924 APPLIC. DATE: 20061222
NATIONAL APPLIC. NO.: US 644924 APPLIC. DATE: 20061222
LANGUAGE: English

Making immunogenic conjugate comprising Streptococcus pneumoniae serotype 3 polysaccharide useful for treating pneumococcal infection, involves periodic acid oxidation of hydrolyzed serotype 3 polysaccharide in presence of bivalent cations - preparation of vaccine comprising polysaccharide-protein conjugate for preventing Streptococcus pneumoniae infection
ABSTRACT: DERWENT ABSTRACT: NOVELTY - Making an immunogenic conjugate comprising Streptococcus pneumoniae serotype 3 polysaccharide covalently linked to a carrier protein involves reacting purified serotype 3 polysaccharide with a mild acid; reacting hydrolyzed serotype 3 polysaccharide with an oxidizing agent in presence of bivalent cations; compounding activated serotype 3 polysaccharide with a carrier protein; reacting the compounded, activated serotype 3 polysaccharide and carrier protein with a reducing agent; and capping unreacted aldehydes in serotype 3 polysaccharide-carrier protein conjugate. DETAILED DESCRIPTION - Making an immunogenic conjugate comprising Streptococcus pneumoniae serotype 3 polysaccharide covalently linked to a carrier protein involves reacting purified serotype 3 polysaccharide with a mild acid resulting in a hydrolyzed serotype 3 polysaccharide; reacting the hydrolyzed serotype 3 polysaccharide with an oxidizing agent in presence of bivalent cations resulting in an activated serotype 3 polysaccharide; compounding the activated serotype 3 polysaccharide with a carrier protein; reacting the compounded, activated serotype 3 polysaccharide and carrier protein with a reducing agent resulting in a serotype 3 polysaccharide-carrier protein conjugate; and capping unreacted aldehydes in the serotype 3 polysaccharide- carrier protein conjugate . WIDER DISCLOSURE - Also disclosed is an immunogenic composition having polysaccharide-protein conjugates of Streptococcus pneumoniae serotype 1, 4, 5 , 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F and optionally an aluminum based adjuvant. ACTIVITY - Antimicrobial; Antibacterial. No biological data is given.MECHANISM OF ACTION - Vaccine. USE - For making an immunogenic conjugate (claimed) useful in immunogenic composition e.g.

vaccine for treating or protecting a human susceptible to pneumococcal infection. ADMINISTRATION - Administration is systemically, mucosally, intramuscularly, intraperitonealy, intradermally, subcutaneously, intranasally, or by injection. Dosage is 0.1-100 (preferably 0.1-10, especially 5) micrograms. ADVANTAGE - Unlike the prior art attempts to produce a multivalent pneumococcal conjugate vaccine that exhibits significant immunogenicity with respect to serotype 3 polysaccharides, this method is improved and provides pneumococcal conjugate vaccine capable of eliciting an immunogenic response to serotype 3 polysaccharides. The conjugate shows increased coverage against pneumococcal diseases in infants and young children globally. EXAMPLE - No suitable example is given.(26 pages)
DESCRIPTORS: Streptococcus pneumoniae, polysaccharide-protein conjugate, adjuvant, appl. vaccine prep., bacterium infection prevention antimicrobial antiseptic bacterium (26, 50)

14/3,K/19 (Item 3 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0431416 DBR Accession No.: 2007-17723 PATENT
New immunogenic composition comprises Streptococcus pneumoniae capsular saccharide conjugates from serotypes 19A and 19F, useful for treating or preventing S. pneumoniae infection, e.g. pneumonia or otitis media - involving vector-mediated gene transfer and expression in host cell
AUTHOR: BIEMANS R L; GARCON N M; HERMAND P V; POOLMAN J; VAN MECHELEN M P
PATENT ASSIGNEE: GLAXOSMITHKLINE BIOLOGICALS SA 2007
PATENT NUMBER: WO 200771710 PATENT DATE: 20070628 WPI ACCESSION NO.: 2007-507772 (200749)
PRIORITY APPLIC. NO.: WO 2006GB004634 APPLIC. DATE: 20061212
NATIONAL APPLIC. NO.: WO 2006EP69977 APPLIC. DATE: 20061220
LANGUAGE: English

New immunogenic composition comprises Streptococcus pneumoniae capsular saccharide conjugates from serotypes 19A and 19F, useful for treating or preventing S. pneumoniae infection, e.g. pneumonia or otitis media - involving vector-mediated gene transfer and expression in host cell
ABSTRACT: DERWENT ABSTRACT: NOVELTY - An immunogenic composition comprising S. pneumoniae capsular saccharide conjugates from serotypes 19A and 19F, where 19A is conjugated to a first bacterial toxoid and 19F is conjugated to a second bacterial toxoid, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for: (1) a vaccine kit comprising the immunogenic composition and further comprising for concomitant or sequential administration an adjuvant; (2) a vaccine comprising the immunogenic composition and a pharmaceutical excipient; (3) a process for making the vaccine comprising mixing the immunogenic composition with a pharmaceutical excipient; (4) a method of immunizing a human host against disease caused by S. pneumoniae infection; (5) a method of eliciting a protective immune response in infants against otitis media; and (6) a method of eliciting a protective immune response to infants or elderly against S. pneumoniae . BIOTECHNOLOGY - Preferred Composition: The first bacterial toxoid is a different protein to the second bacterial...

... toxoids are selected from tetanus toxoid, diphtheria toxoid, CRM197, pertussis toxoid, a bacterial cytolysin, or pneumolysin . Preferably, the first bacterial toxoid is pneumolysin, and the

second bacterial toxoid is diphtheria toxoid. The immunogenic composition further comprises conjugates of S. pneumoniae capsular saccharides 3, 4, 6A, 6B, 9V, 14, 18C, 23F, 1, 5, 7F, or 22F. In the composition above, 2-5 different carrier proteins are separately conjugated to at least 2 different S. pneumoniae capsular saccharide serotypes. The immunogenic composition comprises S. pneumoniae capsular saccharide 1, 3, 4, 5, 6B, 7F, 9V, 14, 23F, 18C, 19A, or 22F conjugated to protein D, pneumolysin, PhtD, or its fusion protein. The immunogenic composition comprises S. pneumoniae capsular saccharide 6A conjugated to pneumolysin or a Haemophilus influenzae protein, optionally protein D or PhtD or fusion protein. The 19A capsular saccharide is directly conjugated to the carrier protein via a linker, where the linker is ADH. It is attached to the carrier protein by carbodiimide chemistry, optionally using EDAC. The 19A saccharide is also conjugated to the carrier protein or to the linker using CDAP chemistry. The ratio of carrier protein to 19A saccharide is 5:1-1:5, 4:1-1:1, or 3.5:1-2.5:1 (w/w). The immunogenic composition comprises a 22F capsular saccharide directly conjugated to the carrier protein via a linker. It is also conjugated to the carrier protein or to the linker using CDAP chemistry. The ratio of carrier protein to 22F saccharide is 5:1-1:5, 4:1-1:1, or 2:1-1:1 (w/w). The average size of the 19A saccharide is above 100 kDa, preferably 110-700 KDa. The 19A saccharide is either a native polysaccharide or is sized by a factor of no more than x5. It has also been sized by microfluidization. The dose of the 19A saccharide conjugate is 1 -10 micrograms, preferably 3 micrograms. The immunogenic composition comprises a 22F saccharide conjugate , where the average size of the 22F saccharide is above 100 kDa, preferably 110-700...

... x5. It has also been sized by microfluidization. The immunogenic composition comprises a 22F saccharide conjugate, where the dose of the 22F saccharide conjugate is 1 -10 micrograms, preferably 3 micrograms of saccharide. The immunogenic composition comprises serotype 1 having an average saccharide size of 300-400 kDa; serotype 4 having an average saccharide size of 75-125 kDa; serotype 5 having an average saccharide size of 350-450 kDa; serotype 6B having an average saccharide size of 1000-1400 kDa; serotype 7F having an average saccharide size of 200-300 kDa; serotype 9V having an average saccharide size of 250-300 kDa; serotype 14 having an average saccharide size of 200-250 kDa; and serotype 23F having an average saccharide size of 900-1000 kDa. The immunogenic composition comprises serotypes 5, 6B, and 23F (and optionally 6A) as native saccharides. It also comprises conjugates of serotypes 4, 18C, 19F and 22F (9 and optionally 19A) at dosages of 3 micrograms of saccharide per conjugate. The immunogenic composition comprises conjugates of serotypes 1, 5, QB, 7F, QV, 14, and 23F (and optionally 6A and/or 3) at dosages of 1 micrograms of saccharide per conjugate. The immunogenic composition comprises unconjugated S. pneumoniae saccharides of serotypes different from those conjugated, so that the number of conjugated and unconjugated saccharide serotypes is less than or equal to 23. The immunogenic composition comprises one or more unconjugated or conjugated S. pneumoniae proteins. The S. pneumoniae proteins are selected from Poly Histidine Triad family (PhtX), Choline

Binding Protein family (CbpX), CbpX truncates, LytX family, LytX truncates, CbpX truncate-LytX truncate chimeric proteins, detoxified pneumolysin (Ply), PspA, PsaA, Sp128, Sp101, Sp130, Sp125, or Sp133. The immunogenic composition comprises pneumolysin or PhtX protein as free or carrier protein. The PhtX protein is PhtD, PhtBD, or ...

... and lipid A derivative, or an oil-in-water emulsion. The adjuvant comprises (per 0.5 ml dose) 0.1-10 mg phospholipid (for instance DOPC); 0.025-2.5 mg sterol (for instance cholesterol); 5-60 micrograms lipid A derivative (for instance 3D-MPL); 5 -60 micrograms saponin (for instance QS21); 0.5 -15 mg metabolizable oil (such as squalene); 0.1-10 mg emulsifier (such as Tween 80); 0.5 -20 mg tocol (such as alpha tocopherol); or 100-750 micrograms Al as aluminum phosphate...

... also comprises a sugar, optionally sucrose. Specifically, the immunogenic composition comprises at least four S. pneumoniae capsular saccharide conjugates containing saccharides from different S. pneumoniae serotypes, where at least one saccharide is conjugated to PhtD or fusion protein, and the immunogenic composition is capable of eliciting an immune response against PhtD. Preferred Method: Immunizing a human host against disease caused by S. pneumoniae infection comprises administering to the host an immunoprotective dose of the immunogenic composition or vaccine. The human host is elderly, and the disease is pneumonia, invasive pneumococcal disease, or exacerbations of chronic obstructive pulmonary disease. The human host is infant, and the disease is otitis media, meningitis and/or bacteremia, or pneumonia and/or conjunctivitis. Eliciting a protective immune response in infants against otitis media comprises the...

... or vaccine, and (b) Protein D from H. influenzae which may be free and/or conjugated . Eliciting a protective immune response to infants against S. pneumoniae comprises administering the immunogenic composition or vaccine above. Eliciting a protective immune response to the elderly against S. pneumoniae comprises administering in combination, sequentially, or concomitantly (a) the immunogenic composition or vaccine, and (b) one or more S. pneumoniae surface proteins selected from PhtX family or pneumolysin . The immunogenic composition or vaccine comprises saccharide conjugates derived from at least all the following serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, where the GMC antibody titer induced against one or more of the vaccine components 4, 6B , 9V, 14, 18C, 19F and 23F is not significantly inferior to that induced by the Prevnar(RTM: Not defined) vaccine in human vaccines. The immunogenic composition comprises a serotype 3, 6A, 19A, or 22F saccharide conjugate. ACTIVITY - Antibacterial; Antiinflammatory; Respiratory-Gen; Auditory; Neuroprotective; Ophthalmological. No biological data given. MECHANISM OF ACTION...

... composition or vaccine is useful for the treatment or prevention of disease caused by S. pneumoniae infection, or in the manufacture of a medicament for the treatment or prevention of diseases caused by S. pneumoniae infection. The disease is pneumonia, invasive pneumococcal disease (IPD), or chronic obstructive pulmonary disease (COPD) of elderly humans. The disease is otitis media, meningitis and/or bacteremia, or conjunctivitis of infant humans (all claimed). ADMINISTRATION - Dosage is 1 -100 micrograms. The administration can be through intramuscular, intraperitoneal, intradermal, subcutaneous, or mucosal route. EXAMPLE...

DESCRIPTORS: Streptococcus pneumoniae recombinant capsular saccharide prep., isol., vector-mediated gene transfer, expression in host cell, antibody, appl., S. pneumoniae infection prevention, therapy antiinflammatory neuroprotective DNA sequence protein sequence (26, 35)

14/3,K/20 (Item 4 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0431295 DBR Accession No.: 2007-17602 PATENT
New immunogenic composition for infants comprises multivalent Streptococcus pneumoniae vaccine comprising capsular saccharide conjugates from different serotypes, useful for treating or preventing S. pneumoniae infection in infants - involving vector-mediated gene transfer and expression in host cell for use in therapy
AUTHOR: BIEMANS R L; GARCON N M; HERMAND P V; POOLMAN J; VAN MECHELEN M P
PATENT ASSIGNEE: GLAXOSMITHKLINE BIOLOGICALS SA 2007
PATENT NUMBER: WO 200771711 PATENT DATE: 20070628 WPI ACCESSION NO.: 2007-507773 (200749)
PRIORITY APPLIC. NO.: WO 2006GB004634 APPLIC. DATE: 20061212
NATIONAL APPLIC. NO.: WO 2006EP69979 APPLIC. DATE: 20061220
LANGUAGE: English

New immunogenic composition for infants comprises multivalent Streptococcus pneumoniae vaccine comprising capsular saccharide conjugates from different serotypes, useful for treating or preventing S. pneumoniae infection in infants - involving vector-mediated gene transfer and expression in host cell for use...
ABSTRACT: DERWENT ABSTRACT: NOVELTY - An immunogenic composition for infants comprising a multivalent S. pneumoniae vaccine comprising 2-15 capsular saccharide conjugates from different serotypes, where the composition comprises a serotype 22F saccharide conjugate, is new. DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for: (1) a vaccine kit comprising an immunogenic composition and further comprising for concomitant or sequential administration an adjuvant; (2) a vaccine comprising the immunogenic composition and a pharmaceutical excipient; (3) a process for making the vaccine comprising mixing the immunogenic composition with a pharmaceutical excipient; (4) a method of immunizing a human host against disease caused by S. pneumoniae infection; (5) a method of eliciting a protective immune response in infants against otitis media; (6) a method of eliciting a protective immune response to infants or elderly against S. pneumoniae; and (7) a method of preventing an elderly human host from having a pneumococcal disease caused by S. pneumoniae serotype 22F infection (or reducing its severity). BIOTECHNOLOGY - Preferred Composition: The immunogenic composition comprises S. pneumoniae capsular saccharide conjugates from serotypes 19A and/or 19F. It comprises S. pneumoniae capsular saccharide conjugates from serotypes 19A and 19F, where 19A is conjugated to a carrier protein, which is a first bacterial toxoid and 19F is conjugated to a second bacterial toxoid. The first bacterial toxoid is a different protein to the...

... toxoids are selected from tetanus toxoid, diphtheria toxoid, CRM197, pertussis toxoid, a bacterial cytolysin, or pneumolysin . Preferably, the first bacterial toxoid is pneumolysin, and the second bacterial toxoid is diphtheria toxoid. The immunogenic composition further comprises conjugates of S. pneumoniae capsular saccharides 1, 4, 5, 6B, 7F,

9V, 14, 18C, and 23F . The immunogenic composition further comprises a S. pneumoniae capsular saccharide 3 or 6A conjugate. In the composition, 2-5 different carrier proteins are separately conjugated to at least 2 different S. pneumoniae capsular saccharide serotypes. The immunogenic composition comprises 2 or more of the carrier proteins selected from tetanus toxoid, diphtheria toxoid, pneumolysin, Protein D, PhtD, or its fusion proteins. The immunogenic composition comprises S. pneumoniae capsular saccharide 1, 3, 4, 5, 6B, 7F, 9V, 14, 23F, 18C, 19A, or 22F conjugated to protein D, pneumolysin , PhtD, tetanus toxoid, or fusion protein. The immunogenic composition comprises S. pneumoniae capsular saccharide 6A conjugated to pneumolysin or a Haemophilus influenzae protein, optionally protein D or PhtD or fusion protein. It also comprises a 19A capsular saccharide directly conjugated to the carrier protein. The 19A capsular saccharide is conjugated to the carrier protein via a linker, where the linker is ADH. It is attached to the carrier protein by carbodiimide chemistry, preferably using EDAC. It is also conjugated to the carrier protein or to the linker using CDAP chemistry. The immunogenic composition comprises a serotype 19A conjugate where the ratio of carrier protein to 19A saccharide is 5:1-1:5, 4: 1-1:1, or 3.5:1-2.5:1 (w/w). The immunogenic composition also comprises a 19F capsular saccharide directly conjugated to the carrier protein, where the ratio of carrier protein to 19F saccharide is 5:1-1: 5, 4:1-1:1, 2:1-1:1, or 1.5:1-1.4:1 . The immunogenic composition also comprises a 22F capsular saccharide directly conjugated to the carrier protein via a linker or using CDAP chemistry, and where the ratio of carrier protein to 22F saccharide is 5:1-1:5, 4:1-1:1, or 2: 1-1:1 (w/w). The average size (e.g. MW) of the 19A saccharide is above 100 kDa, preferably 140-160 kDa. The 19A saccharide is either a native polysaccharide or is sized by a factor of no more than x5. It has also been sized by microfluidization. The immunogenic composition comprises a serotype 19A saccharide conjugate, where the dose of the 19A saccharide conjugate is 1-10 micrograms, preferably 3 micrograms of saccharide. The immunogenic composition comprises a 22F saccharide conjugate, where the average size (e.g. MW) of the 22F saccharide is above 100 kDa...

... It has also been sized by microfluidization, and where the dose of the 22F saccharide conjugate is 1-10 micrograms, preferably 3 micrograms of saccharide. The immunogenic composition comprises serotype 1 (saccharide conjugate) having an average saccharide size (e.g. MW) of 100-1000, preferably 300-400 kDa; serotype 4 having an average saccharide size (e.g. MW) of 50-500, preferably 75-125 kDa; serotype 5 having an average saccharide size (e.g. MW) of 100-1000, preferably 350-450 kDa; serotype 6B having an average saccharide size (e.g. MW) of 500-1600, preferably 1000-1400 kDa; serotype 7F having an average saccharide size (e.g. MW) of 50-1000, preferably 200-300 kDa; serotype 9V having an average saccharide size (e.g. MW) of 50-1000, preferably 250-300 kDa; serotype 14 having an average saccharide size (e.g. MW) of 50-1000, preferably 200-250 kDa; or serotype 23F having an average saccharide size (e.g. MW) of 500-1500, preferably 900-1000 kDa. The immunogenic composition comprises serotypes 5, 6B and 23F (and optionally 6A) as native saccharides. The immunogenic composition comprises

conjugates of serotypes 4, 18C, 19F, and 22F (and optionally 19A) at dosages of 3 micrograms of saccharide per conjugate. It also comprises conjugates of serotypes 1, 5, 6B, 7F, 9V, 14, and 23F (and optionally 6A and/or 3) at dosages of 1 micrograms of saccharide per conjugate . The immunogenic composition further comprises unconjugated S. pneumoniae saccharides of serotypes different from those conjugated, so that the number of conjugated and unconjugated saccharide serotypes is less than or equal to 23. It also comprises one or more unconjugated or conjugated S. pneumoniae proteins. The S. pneumoniae proteins are selected from Poly Histidine Triad family (PhtX), Choline Binding Protein family (CbpX), CbpX truncates, LytX family, LytX truncates, CbpX truncate-LytX truncate chimeric proteins, detoxified pneumolysin (Ply), PspA, PsaA, Sp128, Sp101, Sp130, Sp125, or Sp133. The immunogenic composition comprises pneumolysin or PhtX protein as free or carrier protein. The PhtX protein is PhtD, PhtBD, or...

... and lipid A derivative, or an oil-in-water emulsion. The adjuvant comprises (per 0.5 ml dose) 0.1-10 mg phospholipid (for instance DOPC); 0.025-2.5 mg sterol (for instance cholesterol); 5-60 micrograms lipid A derivative (for instance 3D-MPL); 5 -60 micrograms saponin (for instance QS21); 0.5 -15 mg metabolizable oil (such as squalene); 0.1-10 mg emulsifier (such as Tween 80); 0.5 -20 mg tocol (such as alpha tocopherol); or 100-750 micrograms Al as aluminum phosphate. Specifically, the immunogenic composition comprises at least four S. pneumoniae capsular saccharide conjugates containing saccharides from different S. pneumoniae serotypes, where at least one saccharide is conjugated to PhtD or fusion protein and the immunogenic composition is capable of eliciting an immune response against PhtD Preferred Method: Immunizing a human host against disease caused by S. pneumoniae infection comprises administering to the host an immunoprotective dose of the immunogenic composition or vaccine above. The human host is elderly, and the disease is pneumonia or invasive pneumococcal disease (IPD), or exacerbations of chronic obstructive pulmonary disease (COPD). The human host is also infant, and the disease is otitis media, meningitis and/or bacteremia, or pneumonia and/or conjunctivitis. Eliciting a protective immune response in infants against otitis media comprises administration...

...b) Protein D from H. influenzas, where the protein D may be free and/or conjugated . Eliciting a protective immune response to infants against S. pneumoniae comprises administering the immunogenic composition or vaccine. Eliciting a protective immune response to the elderly against S. pneumoniae comprises administering in combination, sequentially or concomitantly (a) the immunogenic composition or vaccine, or (b) one or more S. pneumoniae surface proteins selected from PhtX family or pneumolysin . The immunogenic composition or vaccine comprises saccharide conjugates derived from at least all the following serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F , where the GMC antibody titer induced against one or more of the vaccine components 4, 6B, 9V, 14, 18C, 19F and 23F is not significantly inferior to that induced by the Prevnar(RTM: Not defined) vaccine in human vaccines. The immunogenic composition comprises a serotype 3, 6A, 19A, or 22F saccharide conjugate. Preventing an elderly human host from having a pneumococcal disease caused by S. pneumoniae serotype 22F infection (or reducing its severity) comprises administering to an infant host (or an infant...

... composition or vaccine is useful for the treatment or prevention of disease caused by S. pneumoniae infection, or in the manufacture of a medicament for the treatment or prevention of diseases caused by S. pneumoniae infection. The disease is pneumonia, invasive pneumococcal disease (IPD), or chronic obstructive pulmonary disease (COPD) of elderly humans. The disease is otitis...

...of a medicament for the prevention or reduction in severity of a disease caused by serotype 22F S. pneumoniae infection in elderly patients, where an immunoprotective dose of the composition or vaccine is administered to an infant (or infant population) (all claimed). ADMINISTRATION - Dosage is 1-100 micrograms. The administration can be through intramuscular, intraperitoneal, intradermal, subcutaneous, or mucosal route. EXAMPLE...
DESCRIPTORS: Streptococcus pneumoniae recombinant vaccine prep., vector-mediated gene transfer, expression in host cell, appl., pneumonia, invasive pneumococcal disease, chronic obstructive pulmonary disease therapy bacterium (26, 35)

14/3,K/21 (Item 5 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0431294 DBR Accession No.: 2007-17601 PATENT
New Streptococcus pneumoniae immunogenic composition comprises capsular saccharides from different S. pneumoniae serotypes, useful for treating or preventing S. pneumoniae infection, e.g. pneumonia or otitis media - involving vector-mediated gene transfer and expression in host cell
AUTHOR: BIEMANS R L; GARCON N M; HERMAND P V; POOLMAN J; VAN MECHELEN M P
PATENT ASSIGNEE: GLAXOSMITHKLINE BIOLOGICALS SA 2007
PATENT NUMBER: WO 200771707 PATENT DATE: 20070628 WPI ACCESSION NO.: 2007-507771 (200749)
PRIORITY APPLIC. NO.: WO 2006GB004634 APPLIC. DATE: 20061212
NATIONAL APPLIC. NO.: WO 2006EP69974 APPLIC. DATE: 20061220
LANGUAGE: English

...ABSTRACT: saccharide is 5:1-1:5, 4:1-1:1, 2:1-1:1, or 1.5: 1-1.4:1 (w/w). The average size (e.g. MW) of the 19F saccharide is above 100...

... than x5. It has also been sized by microfluidization. The dose of the 19F saccharide conjugate is 1-10 micrograms, preferably 1-3 micrograms. At least 8 of the capsular saccharides are conjugated to the same carrier protein, where the carrier protein is not diphtheria toxoid and/or...

... protein D are present as carrier proteins. At least 8 of the capsular saccharides are conjugated to protein D. The composition also comprises capsular saccharide 18C conjugated to TT, optionally where 18C is the only saccharide in the composition conjugated to TT. The 18C capsular saccharide is directly conjugated to the carrier protein via a linker. It is also conjugated to the carrier protein or linker using CDAP chemistry or reductive amination. The ratio of carrier protein to 18C saccharide is 0.5:1-5:1, 1:1-4:1, 1.5:1-3:1, or 2:1-2.5:1 (w/w). The average size (e.g. MW) of the 18C saccharide is above 50 kDa, preferably 50-500 kDa. The 18C saccharide is either a native polysaccharide or is sized by a factor of no more than x5. It has also been sized by microfluidization. The dose

of the 18C saccharide conjugate is 1-10 micrograms, preferably, 3 micrograms. A capsular saccharide conjugate of serotype 6B or 23F is present, but is not conjugated to DT and/or CRM197. The serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F are present as conjugated saccharides, and all are all conjugated to protein D. The immunogenic composition further comprises serotype 3 present as a conjugated saccharide, where the serotype 3 is conjugated to protein D. The immunogenic composition further comprises (conjugated capsular saccharide of) serotype 6A, 15B, 19A, 22F, 8, or 12F. The immunogenic composition comprises serotype 1 (saccharide conjugate) having an average saccharide size (e.g. MW) of 100-1000, preferably 300-400 kDa; serotype 4 having an average saccharide size of 50-500, preferably 75-125 kDa; serotype 5 having an average saccharide size of 100-1000, preferably 350-450 kDa; serotype 6B having an average saccharide size of 500-1600, preferably 1000-1400 kDa; serotype 7F having an average saccharide size of 50-1000, preferably 200-300 kDa; serotype 9V having an average saccharide size of 50-1000, preferably 250-300 kDa; serotype 14 having an average saccharide size of 50-1000, preferably 200-250 kDa; serotype 23F having an average saccharide size of 500-1500, preferably 900-1000 kDa; serotype 19A having an average saccharide size of 50-800 kDa, preferably 140-160 kDa; serotype 22F having an average saccharide size of 50-800 KDa, preferably 150-170 kDa; serotype 6A having an average saccharide size of 500-1600 kDa, preferably 1100-154- kDa; or serotype 3 having an average saccharide size of 50-1000 kDa, preferably 150-250 kDa. The immunogenic composition comprises serotypes 5, 6B, and 23F as native saccharides. It also comprises conjugates of serotypes 4, 18C, and 19F at dosages of 3 micrograms of saccharide per conjugate. It further comprises conjugates of serotypes 1, 5, 6B, 7F, 9V, 14, and 23F at dosages of 1 micrograms of saccharide per conjugate. The immunogenic composition comprises conjugates of serotypes 6A and/or 3 at dosages of 1 micrograms of saccharide per conjugate. It also comprises conjugates of serotypes 19A and/or 22F at dosages of 3 micrograms of saccharide per conjugate . The immunogenic composition further comprises unconjugated S. pneumoniae saccharides of serotypes different from those conjugated, so that the number of conjugated and unconjugated saccharide serotypes is less than or equal to 23. It also comprises one or more unconjugated or conjugated S. pneumoniae proteins. The S. pneumoniae proteins are selected from Poly Histidine Triad family (PhtX), Choline Binding Protein family (CbpX), CbpX truncates, LytX family, LytX truncates, CbpX truncate-LytX truncate chimeric proteins, detoxified pneumolysin (Ply), PspA, PsaA, Sp128, Sp101, Sp130, Sp125, or Sp133. The immunogenic composition comprises pneumolysin or PhtX protein as free or carrier protein. The PhtX protein is PhtD, PhtBD, or ...

... and lipid A derivative, or an oil-in-water emulsion. The adjuvant comprises (per 0.5 ml dose) 0.1-10 mg phospholipid (for instance DOPC); 0.025-2.5 mg sterol (for instance cholesterol); 5-60 micrograms lipid A derivative (for instance 3D-MPL); 5 -60 micrograms saponin (for instance QS21); 0.5 -15 mg metabolizable oil (such as squalene); 0.1-10 mg emulsifier (such as Tween 80); 0.5 -20 mg tocol (such as alpha tocopherol); or 100-750 micrograms Al as aluminum phosphate. Preferred Method: Immunizing a human host against disease caused by S. pneumoniae

infection comprises administering to the host an immunoprotective dose of the immunogenic composition or vaccine. The human host is elderly, and the disease is pneumonia, invasive pneumococcal disease, or exacerbations of chronic obstructive pulmonary disease. The human host is infant, and the disease is otitis media, meningitis and/or bacteremia, or pneumonia and/or conjunctivitis. Specifically, immunizing a human host against disease caused by S. pneumoniae serotype 19A infection comprises administering to the host an immunoprotective dose of the immunogenic composition or vaccine, which comprises a capsular saccharide conjugate of serotype 19F but does not comprise capsular saccharide from serotype 19A. Eliciting a protective immune response in infants against otitis media comprises the administration as separate...

... or vaccine, and (b) Protein D from H. influenzae which may be free and/or conjugated. Alternatively, eliciting a protective immune response to infants against otitis media comprises administering the immunogenic...

... or combined components, sequentially or concomitantly (a) the vaccine, or (b) one or more S. pneumoniae surface proteins selected from PhtX family and pneumolysin . The immunogenic composition or vaccine comprises saccharide conjugates derived from at least all the following serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, 7F, where the GMC antibody titer induced against one or more of the vaccine components 4, 6B, 9V, 14, 18C, 19F and 23F is not significantly inferior to that induced by the Prevnar(RTM: Not defined) vaccine in human vaccines. The immunogenic composition comprises a serotype 3, 6A, 19A , or 22F saccharide conjugate. Eliciting a protective immune response to infants against S. pneumoniae comprises administering the immunogenic composition or vaccine above. Eliciting a protective immune response to the elderly against S. pneumoniae comprises administering in combination, sequentially, or concomitantly (a) the immunogenic composition or vaccine, and (b) one or more S. pneumoniae surface proteins selected from PhtX family or pneumolysin . ACTIVITY - Antibacterial; Antiinflammatory; Respiratory-Gen; Auditory; Neuroprotective; Ophthalmological. No biological data given. MECHANISM OF ACTION...

... composition or vaccine is useful for the treatment or prevention of disease caused by S. pneumoniae infection, or in the manufacture of a medicament for the treatment or prevention of diseases caused by S. pneumoniae infection. The disease is pneumonia, invasive pneumococcal disease (IPD), or chronic obstructive pulmonary disease (COPD) of elderly humans. The disease is otitis media, meningitis and/or bacteremia, or conjunctivitis of infant humans (all claimed). ADMINISTRATION - Dosage is 1 -100 micrograms. The administration can be through intramuscular, intraperitoneal, intradermal, subcutaneous, or mucosal route. EXAMPLE...

14/3,K/22 (Item 6 from file: 357)
DIALOG(R)File 357:Derwent Biotech Res.

0290223 DBR Accession No.: 2002-12070 PATENT
Vaccine for protecting host against disease caused by Bordetella pertussis, Haemophilus influenzae, hepatitis B virus, has conjugate of capsular polysaccharide of H. influenzae and two or more bacterial polysaccharides - Neisseria meningitidis antigen, tetanus toxoid,

diphtheria toxoid, hepatitis B virus surface antigen, recombinant diphtheria toxin carrier protein conjugation for vaccine and infection therapy
AUTHOR: BOUTRIAU D; CAPIAU C; DESMONS P M; LEMOINE D; POOLMAN J
PATENT ASSIGNEE: SMITHKLINE BEECHAM BIOLOGICALS 2002
PATENT NUMBER: WO 200200249 PATENT DATE: 20020103 WPI ACCESSION NO.: 2002-280437 (200232)
PRIORITY APPLIC. NO.: GB 20018364 APPLIC. DATE: 20010403
NATIONAL APPLIC. NO.: WO 2001EP7288 APPLIC. DATE: 20010627
LANGUAGE: English

...for protecting host against disease caused by Bordetella pertussis, Haemophilus influenzae, hepatitis B virus, has conjugate of capsular polysaccharide of H. influenzae and two or more bacterial polysaccharides - Neisseria meningitidis antigen, tetanus toxoid, diphtheria toxoid, hepatitis B virus surface antigen, recombinant diphtheria toxin carrier protein conjugation for vaccine and infection therapy
ABSTRACT: DERWENT ABSTRACT: NOVELTY - A multi-valent immunogenic composition (I), comprising conjugate of a carrier protein and capsular polysaccharide (CP) of Haemophilus influenzae type B (HiB) and ...

... to a host against infection by bacteria from which they are derived, where HiB CP conjugate is not adsorbed onto an aluminum adjuvant salt, is new. DETAILED DESCRIPTION - An INDEPENDENT CLAIM...

... acellular pertussis components, tetanus toxoid (TT), diphtheria toxoid (DT), hepatitis B surface antigen (HepB), a conjugate of a carrier protein and the capsular polysaccharide of HiB (where the amount of conjugate per 0.5 ml dose of bulk vaccine is 1-8 micro-g and the immunogenicity of the conjugate is equivalent or improved over such compositions comprising larger amounts of conjugate), and one or more conjugates of a carrier protein and a capsular polysaccharide of a bacterium such as Neisseria meningitidis...

...together the individual components. Preferred Composition: (I) comprises more than 7 further bacterial polysaccharides, preferably pneumococcal CP. None of the polysaccharides in the composition are adsorbed onto an aluminum adjuvant salt. The bacterial CP are N. meningitidis serogroup A CP (MenA), MenC, MenY or MenW, Streptococcus pneumoniae serotype 1, 2, 3, 4, 5, 6A, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F or 33F CP, Group B Streptococcus group I, II, III, IV or V CP, Staphylococcus aureus type 5 or 8, Vi polysaccharide from Salmonella typhi, N. meningitidis lipopolysaccharide (LPS), M. catarrhalis LPS and H. influenzae LPS. The bacterial CP are conjugated to a carrier protein such as TT, DT, CRM197, recombinant diphtheria toxin, OMPC from N.meningitidis, pneumolysin from S. pneumoniae and protein D from H. influenzae. The CP of HiB and the further polysaccharides are not all conjugated to the same carrier, CRM197. (I) further comprises killed, attenuated hepatitis A virus or inactivated...

... HiB and a plain formulation of MenC-HiB. These three formulations were administered to the 3 first study groups of infants at 3, 4 and 5 months of age. Tritanrix-HepB (RTM) (DT-TT-Pw-HepB vaccine) was given concomitantly (as...
...RTM) and administered as a single injection to the fourth study group of infants at 3, 4 and 5 months of age. The fifth group (control) was administered Tritanrix-HepB (RTM)-HiB vaccine at 3, 4 and 5 months of age. The results showed that each

formulation that was evaluated induced a good...

... a human host against disease caused by the above pathogens (claimed). ADMINISTRATION - The amount of conjugate per 0.5 ml dose of bulk vaccine is 3-6, preferably 5 microg (claimed). Administered by intramuscular, intraperitoneal, intradermal, subcutaneous, mucosal or oral route. ADVANTAGE - (I) is...

... polysaccharide (MenA)-MenC-Haemophilus influenzae type B (HiB) was prepared. MenA and MenC capsular polysaccharide conjugated onto protein D and HiB conjugated onto tetanus toxoid were mixed together in an amount of 5 micro-g of each polysaccharide in each conjugate per 0.5 ml human dose. The pH was adjusted to 6. 1, and was lyophilized in the presence of sucrose.(31 pages)
DESCRIPTORS: Bordetella pertussis, Haemophilus influenzae, Neisseria meningitidis, Streptococcus pneumoniae, Staphylococcus aureus, Salmonella typhi capsular polysaccharide, lipopolysaccharide antigen, tetanus toxoid, diphtheriatoxoid, hepatitis B virus surface antigen, recombinant diphtheria toxin carrier protein conjugation, immunization in human infant, adjuvant, appl. vaccine, Bordetella pertussis, Haemophilus influenzae, Clostridium tetani, Corynebacteriumdiphtheriae, Neisseria...

14/3,K/23 (Item 1 from file: 457)
DIALOG(R)File 457:The Lancet

0000070055
USE FORMAT 7 OR 9 FOR FULL TEXT
The evidence for using conjugate vaccines to protect HIV-infected children against pneumococcal disease
Bliss, Sandra J; O'Brien, Katherine L; Janoff, Edward N; Cotton, Mark F; Musoke, Philippa; Coovadia, Hoosen; Levine, Orin S
The Lancet Infectious Diseases vol. 8, 1 PP: 67-80 Jan 2008
DOCUMENT TYPE: PERIODICAL; General Information LANGUAGE: English
RECORD TYPE: New; Fulltext
LENGTH: 14 Pages
WORD COUNT: 10852

The evidence for using conjugate vaccines to protect HIV-infected children against pneumococcal disease
TEXT:
Pneumococcal conjugate vaccines (PCVs) are a potentially useful complement to existing treatment strategies in HIV-infected children, for whom pneumococcal infections are common and serious. This Review summarises available data on the burden of pneumococcal disease and the safety and efficacy of PCVs in HIV-infected children. The data demonstrate that children with HIV have significantly increased risk of pneumococcal disease compared with uninfected children; the serotypes included in currently licensed or near-licensure conjugate vaccines include most serotypes that cause invasive pneumococcal disease (IPD) in HIV-infected children and adults; PCVs provide substantial protection against IPD and clinical pneumonia when given to HIV-infected infants; and HIV-infected adults gain an indirect benefit when ...

...dysfunction, children with HIV are at high risk of bacterial infections compared with uninfected children.1-3 In the USA, among HIV-infected children, serious bacterial infections occur five times more frequently than other opportunistic infections, such as herpes zoster, disseminated mycobacterial infections, Pneumocystis jirovecii pneumonia, and oesophageal candidiasis." Moreover, serious bacterial

infections occur throughout all stages of HIV disease.7 In particular, individuals with HIV have a risk of bacterial pneumonia up to 25-fold higher than H I V- uninfected people;8 Streptococcus pneumoniae is the most common cause of bacterial pneumonia and is prominent among all serious bacterial infections in this population.4-6-8-27

WHO estimates that between 700000 and 1 million children die of pneumococcal disease every year, most in the developing world.28 In countries where pneumococcal conjugate vaccine (PCV) has been routinely used in infancy, rates of invasive pneumococcal disease (IPD) have reduced by up to 75% in children and up to 29% in...

...in children and adults with HIV are clearly needed. We review the existing evidence on pneumococcal disease risk and the effects of pneumococcal conjugate vaccination in HIV-infected people to determine whether a policy for routine PCV use in areas with a substantial burden of HIV infection should be advised.

Burden of pneumococcal disease in HIV-infected people

Many parts of the world have surveillance systems for the identification of IPD, defined as isolation of S pneumoniae from a normally sterile site. However, in resource-poor countries, accurate information on the burden of serious pneumococcal infections is often unavailable. Children with invasive disease may not present to medical attention, clinical...

...limited by antibiotic pretreatment. Even where comprehensive surveillance systems are established, the true burden of pneumococcal disease is much greater than that estimated by invasive disease surveillance. Non-bacteraemic pneumococcal pneumonia is estimated to be at least ten-fold more common than IPD.33-37 Therefore...
...IPD estimates, particularly in the developing world, will typically underestimate the true scope of severe pneumococcal infection. Bacteraemia may be more common in HIV-infected people with pneumococcal pneumonia than among HIV-uninfected people,1 ,38 and studies that report on pneumococcal disease in patients with advanced HIV infection only might not accurately represent the burden of...

...with HIV infection.

In 16 studies from Africa and the USA, the incidence of IPD, pneumococcal bacteraemia, bacteraemic pneumococcal pneumonia, or meningitis in children infected with HIV ranged from 183 to 18 500 episodes of...

...a nine-fold to 43 -fold increase in IPD compared with HIV-uninfected children (table 1),4,6,14,17,18,20,23,39-47 Children with HIV infection are also up to eight...

...Europe, Australia, Asia, and the USA reported incidence rates for HIV-infected adults with IPD, pneumococcal bacteraemia, pneumococcal meningitis, bacteraemic pneumococcal pneumonia, or pneumococcal pneumonia (table 2).7,10,24,38,43,50-74 IPD incidence rates among HIV-infected...
...infection than those without.49,61,70,75-77

Impact of HAART on burden of pneumococcal disease in HIV-infected people

The introduction of highly active antiretroviral therapy (HAART) has brought...

...of morbidity and mortality in HIV-infected people. HAART may also be expected to reduce pneumococcal disease burden, through improvements in immune function and through reduced rates of pneumococcal colonisation.78 In developed countries, epidemiological studies have identified two to three-fold reductions in...

...rates among adults during the HAART era (1996-97 to the present). The incidence of pneumococcal bacteraemia in Spain has declined from 2410 to 820 per 100000 HIV-positive adults since By contrast with adults, one paediatric study found no association between HAART use and pneumococcal colonisation.80 However, epidemiological studies have shown a five-fold reduction in overall pneumonia incidence (from 11-1 to 2-15 per 100 person-years; p<0.001),81 a nine-fold reduction in incidence of bacteraemia (from 3.3 to 0-35 per 100 person-years; p<0.001),81 and a substantial reduction in hospital admissions for pneumonia82 in children between the pre-HAART and HAART eras. Additionally, the lowest reported IPD rate...

...children, and the ability to deliver HAART to them.

Mortality in HIV-infected individuals with pneumococcal disease

In ten studies, mortality from IPD in children infected with HIV ranged between zero and 23-3% (webtable 1), with case fatality rates similar to those among HIVuninfected children (0-15 -2%)4,14 ,18,23,25,42-44,83,84 However, in these studies, differences between HIV-infected...

...85-87 and mortality was as high as 57% for adults with AIDS and bacteraemic pneumococcal pneumonia.87 Where patients were stratified by clinical status, patients with AIDS had far higher mortality ...

...than those with HIV infection but not AIDS (0-7%).53,61,87,93

In 14 studies that directly compared mortality between HIV-infected and HIV-uninfected individuals, more studies found...

...a heightened inflammatory response.68

Proportion of IPD in HIV-infected people caused by the conjugate vaccine serotypes

Since PCVs only protect against disease caused by serotypes included in the vaccine...

...the serotypes in the vaccine to those causing disease locally. The currently licensed seven-valent conjugate vaccine includes capsular polysaccharides from seven serotypes (4, 6B, 9V, 14 , 18C, 19F, and 23F). Other vaccine candidates evaluated include frve-valent (serotypes 6B, 14, 18C, 19F, and 23F), nine-valent (seven-valent plus serotypes 1 and 5), ten- valent (nine-valent plus serotype 7F), 11-valent (ten-valent plus serotype 3), and 13-valent (11-valent plus serotypes 19A and 6A) formulations.

Only the five, seven, and nine-valent vaccines have been used in studies in...

...than in the USA, Europe, and Africa, particularly when the vaccine does not include serotypes 1 and 5.98

Eight studies from South Africa and the USA reported on serotype /serogroup coverage of isolates causing invasive disease in children with HIV infection (webtable 3).18,31,41-44,99,100 In the USA, seven-valent conjugate vaccine included 85-93% of invasive isolates among HIV-infected children, and in South Africa...HIV-infected and uninfected children. No studies have reported on the impact of HAART on serotype distribution.

In ten studies from South Africa, Spain, and the USA, a broader distribution of serotypes cause invasive disease in adults than children, so conjugate vaccine coverage of invasive isolates is lower among adults (17-66%, webtable 4).32,43,59,61,89,99,101-103 However, most of the identified studies found...

...and a higher absolute burden) of IPD caused by isolates that are

included in the conjugate vaccines compared with HIV-uninfected adults (figure). Increased antibiotic use among HIV-infected adults might ...

...proximity to small children.101 These findings provide a foundation for the hypothesis that routine conjugate vaccination of children might reduce pneumococcal disease burden for the HIV-infected adult members of their families and community. No study looked at the effect of HAART on serotype distribution in HIV-infected adults; however, a study spanning the pre-HAART and HAART eras found no change in serotype distribution over time.69

Safety of PCVs in HIV-infected children

Five different PCVs have...

...of serious reports after PCV administration is no different than with other currently licensed vaccines (1-9 serious events per 100000 doses).112

Five studies from the USA and South Africa...

...the safety of PCV specifically among HIV-infected children.108,113-116 One study compared pneumococcal polysaccharide vaccination to conjugate vaccination in children older than 2 years of age and found no difference in adverse...

...children older than 2 years found a 7% rate (15 of 225 patients) of grade 3 or higher adverse reactions, most of which were local reactions, with no life-threatening adverse...

...39000 children, of whom more than 2500 were estimated to be HIV positive, found the conjugate vaccine to be well tolerated compared with placebo.108 A higher rate of asthma was...

...in CD4-cell counts, or disease progression,117 although ongoing vigilance is warranted, since a pneumococcal polysaccharide vaccine trial in HIV-infected adults in the developing world showed a paradoxically increased rate of pneumonia among vaccine recipients.60 5 -year follow-up of HIV-infected children enrolled in a South African efficacy study found a lower CD4 percentage among PCV recipients compared with placebo recipients (12 . 6% vs 16-1%, p=0 , 04) and a non-significant difference in mean CD4-cell counts (493 cells...

...HIV-infected adults found no short-term or long-term increases in viral load after conjugate vaccine administration.119120

Immunogenicity of PCVs in HIV-infected children

To address a lack of...

...efficacy against IPD.121 No consensus correlate of immunity has been determined for non-invasive pneumococcal disease, nor is there consensus on a concentration estimate that correlates with clinical efficacy in...

...Spain, and the USA report on the immunogenicity of PCV in HIV-infected children (table 3)113,116,118,122-125 The studies varied substantially with respect to the immunological endpoints...

...uninfected children. These studies all assessed PCV using the CRM carrier protein; vaccines with different conjugate technology might yield different results.

In six studies that compared responses ...of HAART on quantitative antibody response to PCV found a significant positive association (p=0. 3) between antibody concentration and duration of HAART116 Among children not on antiretroviral therapy, in all...

...antibody response found lower antibody concentrations in HIV-infected

children 8 months, 12 months, and 5 years after the primary PCV immunisation series compared with HIVuninfected children.118,22,24 Further ...

...withholding booster immunisations in settings where HIV is endemic.
In children without HIV infection, quantitative pneumococcal antibody concentrations correlate with both functional antibody measures (ie, opsonophagocytic activity) and clinical efficacy121 However...

...always correlate with functional activity in children infected with HIV125 The functional activity of the pneumococcal antibodies elicited by PCV is lower in HIV-infected than HIV-uninfected children.123 Additionally...

...far, only a South African trial108 measured vaccine efficacy in children infected with HIV (table 4). Overall, the vaccine provided significant protection against vaccine-type invasive disease in HIV-infected children...

...0.003)). PCV was associated with a non-significant 13% (-7% to 29%) reduction in pneumonia and 6% reduction in mortality (p=0.3) in HIV-infected children; by contrast, the 20% (2-35%; p=0.3) reduction in pneumonia for HIV- negative children was significant. As suggested by the immunogenicity studies, 5-year follow-up of this study has shown a greater attenuation in the vaccine efficacy...

...8% (-7-8% to 65-2%)) compared with non-infected children (VE 77 . 8% (34 . 4-92 . 5%)); although a greater efficacy against all serotype IPD was shown in HIV-infected (46-1%) versus uninfected children (35%, p<0.0001).18
When assessing the public-health impact of pneumococcal conjugate vaccination, however, it is useful to consider the efficacy of the vaccine in absolute terms...

...absolute rate reductions were demonstrated in the South African trial by using different definitions of pneumonia.126 Whereas the point estimate for vaccine efficacy for HIV-infected children was higher for bacteraemic pneumococcal pneumonia (45% (1-70%)) than for a clinical diagnosis of lower respiratory tract infection (15% (6-24%)), the...

...lower respiratory tract infections (2573 cases prevented per 100000 childyears versus 483 episodes of bacteraemic pneumococcal pneumonia prevented per 100000 child -years), because clinical pneumonia is several times more frequent than bacteraemic pneumococcal pneumonia.126 Similarly, whereas vaccine efficacy against vaccine-type IPD is lower in HIV-infected than...

...uninfected children (2250 vs 38 cases prevented per 100000 child -years) .118
Indirect effects of pneumococcal disease
PCVs reduce the prevalence of vaccine-type pneumococcal carriage in vaccinated children. This effect in turn reduces the likelihood that vaccine-type pneumococci will be transmitted from vaccinated children to unvaccinated contacts, providing the basis for herd immunity. Nasopharyngeal colonisation studies have found higher rates of pneumococcal carriage in adults who live with young children127 than in adults who do not, and...

...risk of IPD in adults and contact with young children.128 Declines in vaccine-type pneumococcal colonisation have been seen among non-immunised adults - for example, in Alaskan natives, the proportion of adult pneumococcal carriers with vaccine-type colonisation decreased

from 28% to 4-5% (78 of 275 carriers to 17 of 377 carriers) after introduction of PCV in children aged under 5 years.129

An indirect effect on invasive disease has been seen in countries where conjugate vaccination strategies have been widely implemented in children aged under 5 years. In the USA, rates of vaccine-type IPD declined by 62% among people aged 5 years and older between 1998-99 and 2003. 29 In Canada, there was a 62...

...absolute terms, more cases of vaccine-type IPD were prevented in the USA among individuals 5 years and older than among the population targeted for vaccination (20459 vs 9140 cases).29 An additional benefit of PCV has been the reduction of pneumococcal disease caused by antibiotic-resistant strains, many of which are included in the conjugate vaccine.131

The impact of vaccination on pneumococcal transmission and colonisation in communities burdened with substantial rates of HIV infection is less clearly understood. Most studies indicate that the prevalence of pneumococcal colonisation is similar among HIV-infected and HIV-uninfected children and adults.2132134 The duration...
...In settings with a high burden of HIV, the magnitude of the indirect benefit from conjugate vaccination of children to HIV-infected adult members of the community may be diminished because of an expanded role of older HIV-infected children and adults in pneumococcal transmission, and because of reduced mucosal immunogenicity of PCV in children with HIV, although data...

...the USA aged 18-64 years with HIV/ AIDS have shown an indirect benefit of conjugate vaccination since it was introduced in children in 2000. Between 1998-99 and 2003, the...

...seen, a potentially important finding in a population with greater antibiotic exposure.135

Effects of serotype replacement on the benefits of PCVs in HIV-infected people

In addition to reducing vaccine...

...the USA, surveillance data since 1994 show that increases in the rate of non-vaccine serotype invasive disease have occurred, attenuating the overall impact of vaccination; however, the increase in non...

...disease.139 Specifically, when comparing rates in 2003 to pre-vaccine era rates, non-vaccine serotype IPD cases increased by approximately 4700 cases whereas vaccineserotype IPD decreased by 29600 cases annually...

...Disease Control and Prevention (CDC) is too small to draw any conclusions with respect to serotype replacement among this group (Whitney C, CDC, Atlanta, GA; personal communication). Long-term follow-up ...

...trial showed a non-significant 27% (-80-2 to 70-6%) increase in non-vaccine serotype IPD in vaccinated HIV-infected children compared with unvaccinated HIVinfected children; this still compares favourably...

...among uninfected participants.118

Among 18-64-year-old HIV-infected adults in the USA, serotype replacement has reduced the indirect benefit of conjugate vaccination, with a 44% increase in non-vaccine -type invasive disease.135 Serotype replacement disease was not seen among HIV-infected white men; therefore, the percent IPD rate...

...still prevented in black men than in white men.135 In defining implications for future pneumococcal disease risk, ongoing surveillance will be crucial to determine if these trends (particularly

with respect to serotype replacement disease among HIV-infected people) will continue or plateau.

Cost-effectiveness of pneumococcal conjugate vaccination for HIV-infected children

Many studies in the developed world have been done to...

...as great as the direct benefit to vaccinees, nor did they consider the impact of pneumococcal conjugate vaccination on replacement disease or non-invasive disease such as pneumonia. Analyses of cost-effectiveness might therefore change when these effects are better understood. For example...112000 to $7500.145

One study that did a cost-effectiveness analysis for implementation of pneumococcal conjugate vaccination in the developing world found a cost of $56-112 per life-year saved...

...a cost of $100 per disability-adjusted life year averted at a vaccine cost of $5 per dose; vaccination was projected to be highly cost effective in 68 of 72 countries...

...with a high burden of HIV infection.

Discussion

This Review shows that the incidence of pneumococcal disease in HIV-infected people might be up to 320 times higher than in HIV...

...in all studies that compared rates directly to HIV-negative people. Although HAART may reduce pneumococcal disease, IPD rates still remain high even after the introduction of HAART46 6170 The effect of cotrimoxazole prophylaxis on pneumococcal disease risk is less clear;16,63,64,79,143,144 though any benefit is modest at best.

Two important findings emerge from a review of the serotypes that cause pneumococcal disease among HIV-infected people. First, the serotypes that cause invasive disease are similar among...

...show the potential health impact of vaccination. When measured in absolute terms, the benefits of pneumococcal conjugate vaccination are greatest among those children infected with HIV However, the safety, immunogenicity, and efficacy...

...vaccination among HIV-infected children, since vaccinated children had a lower mean CD4 percentage at 5 years than their unvaccinated peers, and because the vaccine response, although protective, does appear to...

...absolute numbers the benefit to adults may be greater than to children. The magnitude of serotype replacement disease, which will likely attenuate some of the direct and indirect benefits to HIV...

...expected.

Conclusion

In resource-poor countries, the introduction of HAART is expected to reduce the pneumococcal disease burden caused by all serotypes. In view of its safety and efficacy profiles, and...

...and adults. Where it is possible, IPD surveillance should continue to assess the impact of pneumococcal conjugate vaccination on disease burden and serotype replacement in settings with a substantial degree of HIV infection.

Conflicts of interest

KLOB has...

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See Online forwebtablel
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See Online for webtable 3 and webtable 4
Search strategy and selection criteria
Dataforthis Review were identified by searching PubMed using combinations of the following search terms: "pneumococcus", " pneumococcal", "Streptococcus pneumoniae", "conjugate pneumococcal vaccine", "HIV", "human immunodeficiency virus", "AIDS", and "acquired immunodeficiency syndrome". Only English language articles were...

...authors' own files. Articles were included if they provided data for HIV-infected individuals on pneumococcal disease burden (including incidence rates of diseaseand comparisons with HIV-uninfected individuals), case fatality rate, capsular serotype distribution, PCV safety, immunogenicity including quantitative and qualitative assays, vaccine efficacy, absolute disease reduction caused by vaccination, or indirect effects of vaccination on pneumococcal disease burden. For IPD disease burden, serotype distribution, and rates of absolute disease reduction, data were abstracted from the published articles and...
CITED REFERENCES:
References
1 Janoff EN, Breiman RF, Daley CL, Hopewell PC. Pneumococcal disease during HIV infection. Epidemiologic, clinical, and immunologic perspectives. Ann Intern Med 1992; 117: 314-24.
2 Janoff EN, O'Brien J, Thompson P, et al. Streptococcus pneumoniae colonization, bacteremia, and immune response among persons with human immunodeficiency virus infection. J Infect Dis 1993; 167: 49-56.
3 Bernstein LJ, Ochs HD, Wedgwood RJ, Rubinstein A. Defective humoral immunity in pediatric acquired immune deficiency syndrome. J Pediatr 1985; 107: 352-57
4 Andiman WA, Mezger J, Shapiro E. Invasive bacterial infections in children born to women infected with human immunodeficiency virus type 1. J Pediatr 1994; 124: 846-52.
5 Bernstein LJ, Krieger BZ, Novick B, Sicklick MJ, Rubinstein A. Bacterial infection in the acquired immunodeficiency syndrome of children. Pediatr Infect Dis 1985; 4: 472-75.
6 Dankner WM, Lindsey JC, Levin MJ. Correlates of opportunistic infections in children...

...J 2001; 20:40-48.
7 Gilks CF, Ojoo SA, Ojoo JC, et al. Invasive pneumococcal disease in a cohort of predominantly HIV-I infected female sex-workers in Nairobi, Kenya...

...23.
8 Feikin DR, Feldman C, Schuchat A, Janoff EN. Global strategies to prevent bacterial pneumonia in adults with HIV disease. Lancet Infect Dis 2004; 4: 445-55.
9 Archibald LK, McDonald LC, Nwanyanwu O, et al. A hospital-based prevalence...

...2000; 181: 1414-20.
10 Boschini A, Smacchia C, Di FM, et al. Community-acquired pneumonia in a cohort of former injection drug users with and without

human immunodeficiency virus infection...

...1996; 23: 107-13.
11 Falco V, Fernandez de ST, Alegre J, et al. Bacterial pneumonia in HIV-infected patients: a prospective study of 68 episodes. Eur Respir J 1994; 7...

...and mortality among adult medical admissions in Malawi predominance of non-typhi salmonellae and Streptococcus pneumoniae. J Infect 2001; 42: 44-49.
13 Koulla-Shiro S, Kuaban C, Belec L. Acute community-acquired bacterial pneumonia in human immunodeficiency virus (HIV) infected and non-HIV-infected adult patients in Cameroon: aetiology and outcome. Tuber Lung Dis 1996; 77 47-51.
14 Lichenstein R, King JC Jr, Farley JJ, Su P, Nair P, Vink PE. Bacteremia in...

...1998; 17: 381-85.
15 Lopez-Palomo C, Martin- Zamorano M, Benitez E, et al. Pneumonia in HIV-infected patients in the HAART era: incidence, risk, and impact of the pneumococcal vaccination. J Med Virol 2004; 72: 517-24.
16 Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group...

...of bacteria causing severe community-acquired lower respiratory tract infections in human immunodeficiency virus type 1-infected children. Clin Infect Dis 2000; 31: 170-76.
18 Madhi SA, Madhi A, Petersen K, Khoosal M, Klugman KP. Impact of human immunodeficiency virus type 1 infection on the epidemiology and outcome of bacterial meningitis in South African children. Int J Infect Dis 2001; 5: 119-25.
19 Molyneux EM, Tembo M, Kayira K, et al. The effect of HIV...

...Venzon D, Butler K, Husson R, Pizzo PA. Bacterial infections in human immunodeficiency virus type 1-infected children: the impact of central venous catheters and antiretroviral agents. Pediatr Infect Dis J...

...1988; 7: 323-28.
26 Uriyo J, Gosling RD, Maddox V, et al. Prevalences of Pneumocystis jiroveci, Mycobacterium tuberculosis and Streptococcus pneumoniae infection in children with severe pneumonia, in a tertiary referral hospital in northern Tanzania. Ann Trop Med Parasitol 2006; 100: 245...

...Muyodi C, et al. Aetiology, outcome, and risk factors for mortality among adults with acute pneumonia in Kenya. Lancet 2000; 355: 1225-30.
28 WHO. Pneumococcal conjugate vaccine for childhood immunization- WHO position paper. Wkly Epidemiol Ree 2007; 82: 93-104.
29 CDC. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease - United States, 1998-2003. MMWR Morb Mortal Wkly Rep 2005; 54: 893-97
30 Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of proteinpolysaccharide conjugate vaccine. N Engl J Med 2003; 348: 1737-46.
31 Karstaedt AS, Khoosal M, Crewe-Brown HH. Pneumococcal bacteremia during a decade in children in Soweto, South Africa. Pediatr Infect Dis J 2000; 19: 454-57
32 Karstaedt AS, Khoosal M, Crewe-Brown HH. Pneumococcal bacteremia in adults in Soweto, South Africa, during the course of a

decade. Clin Infect Dis 2001; 33: 610-14.
33 Beovic B, Bonac B, Kese D, et al. Aetiology and clinical presentation of mild community-acquired bacterial pneumonia. Eur J Clin Microbiol Infect Dis 2003; 22: 584-91.
34 Ishida T, Hashimoto T, Arita M, Tojo Y, Tachibana H, Jinnai M. A 3-year prospective study of a urinary antigen-detection test for Streptococcus pneumoniae in community-acquired pneumonia: utility and clinical impact on the reported etiology. J Infect Chemother 2004; 10: 359-63...

...et al. Contribution of a urinary antigen assay (Binax NOW) to the early diagnosis of pneumococcal pneumonia. Clin Infect Dis 2004; 38: 222-26.
36 Cutts FT, Zaman SM, Enwere G, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet 2005; 365: 1139-46.
37 Davidson M, Tempest B, Palmer DL. Bacteriologic diagnosis of acute pneumonia. Comparison of sputum, transtracheal aspirates, and lung aspirates. JAMA 1976; 235: 158-63.
38 Garcia-Leoni ME, Moreno S, Rodeno P, Cercenado E, Vicente T, Bouza E. Pneumococcal pneumonia in adult hospitalized patients infected with the human immunodeficiency virus. Arch Intern Med 1992;152...

...39 Farley JJ, King JC Jr, Nair P, Hines SE, Tressler RL, Vink PE. Invasive pneumococcal disease among infected and uninfected children of mothers with human immunodeficiency virus infection. J Pediatr...

...Peters VB, Hyatt AC, Schechter C, Diamant EP, Hodes DS. Evaluation of prophylaxis against invasive pneumococcal infections in human immunodeficiency virus-infected children. Pediatr Infect Dis J 1994; 13: 667-69.
41 Andiman WA, Simpson J, Holtkamp C, Pearson HA. Invasive pneumococcal infections in children infected with HIV are not associated with splenic dysfunction. AIDS Patient Care STDS 1996; 10: 336-41.
42 Mao C, Harper M, Mcintosh K, et al. Invasive pneumococcal infections in human immunodeficiency virus-infected children. J Infect Dis 1996; 173: 870-76.
43...

...Huebner R, Khoosal M, Crewe-Brown H, Klugman K. The impact of HIV on Streptococcus pneumoniae bacteraemia in a South African population. AIDS 1998; 12: 2177-84.
44 Madhi SA, Petersen K, Madhi A, Wasas A, Klugman KP. Impact of human immunodeficiency virus type 1 on the disease spectrum of Streptococcus pneumoniae in South African children. Pediatr Infect Dis J 2000; 19: 1141-47
45 Hughes WT...

...J 2006; 25: 623-27
48 Gesner M, Desiderio D, Kim M, et al. Streptococcus pneumoniae in human immunodeficiency virus type 1-infected children. Pediatr Infect Dis J 1994; 13: 697-703.
49 King MD, Whitney CG, Parekh F, Farley MM. Recurrent invasive pneumococcal disease: a population-based assessment. Clin Infect Dis 2003; 37: 1029-36.
50 Simberkoff MS, El SW, Schiffman G, Rahal JJ Jr. Streptococcus pneumoniae infections and bacteremia in patients with acquired immune deficiency syndrome, with report of a pneumococcal vaccine failure. Am Rev Respir Dis 1984; 130: 1174-76.
51 Polsky B, Gold JW, Whimbey E, et al. Bacterial pneumonia in patients with the acquired immunodeficiency syndrome. Ann Intern Med 1986;

104: 38 1-1.
52 Selwyn PA, Feingold AR, Hartel D, et al. Increased risk of bacterial pneumonia in HIV-infected intravenous drug users without AIDS. AIDS 1988; 2: 267-72.
53 Redd...

...Rutherford GW, III, Sande MA, et al. The role of human immunodeficiency virus infection in pneumococcal bacteremia in San Francisco residents. J Infect Dis 1990; 162: 1012-17
54 Schuchat A, Broome CV, Hightower A, Costa SJ, Parkin W Use of surveillance for invasive pneumococcal disease to estimate the size of the immunosuppressed HIV-infected population. JAMA 1991; 265: 3275...

...Dis 1994; 26: 635-42.
56 Plouffe JF, Breiman RF, Facldam RR. Bacteremia with Streptococcus pneumoniae. Implications for therapy and prevention. Franklin County Pneumonia Study Group. JAMA 1996; 275: 194-98.
57 Almirante B, Saballs M, Ribera E, et...

...Clin Infect Dis 1998; 27: 176-80.
58 Pastor P, Medley F, Murphy TV. Invasive pneumococcal disease in Dallas County, Texas: results from population-based surveillance in 1995. Clin Infect Dis 1998; 26: 590-95.
59 Feldman C, Glatthaar M, Morar R, et al. Bacteremic pneumococcal pneumonia in HIV-seropositive and HIV-seronegative adults. Chest 1999; 116: 107-14.
60 French N, Nakiyingi J, Carpenter LM, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. Lancet 2000; 355:2106-11...

...JC, Gelling L, Kool JL, Reingold AL, Vugia DJ. Epidemiologic relation between HIV and invasive pneumococcal disease in San Francisco County, California. Ann Intern Med 2000; 132: 182-90.
62 Attia A, Huet C, Anglaret X, et al. HIV-1-related morbidity in adults, Abidjan, Cote d'Ivoire: a nidus for bacterial diseases. J Acquir...
...2001; 28:478-86.
63 Dworkin MS, Ward JW, Hanson DL, Jones JL, Kaplan JE. Pneumococcal disease among human immunodeficiency virus-infected persons: incidence, risk factors, and impact of vaccination. Clin...Infect Dis 2001; 33: 393-98.
65 Pierce AB, Hoy JF. Is the recommendation for pneumococcal vaccination of HIV patients evidence based? J Clin Virol 2001; 22: 255-61.
66 Allen SH, Brennan-Benson P, Nelson M, et al. Pneumonia due to antibiotic resistant Streptococcus pneumoniae and Pseudomonas aeruginosa in the HAART era. Postgrad Med J 2003; 79: 691-94.
67...

...SM, Hsiao CF, Sheng WH, Chang SC. Clinical experience of the 23-valent capsular polysaccharide pneumococcal vaccination in HIV-1 -infected patients receiving highly active antiretroviral therapy: a prospective observational study. Vaccine 2004; 22: 2006-12.
68 Jordano Q, Falco V, Almirante B, et al. Invasive pneumococcal disease in patients infected with HIV still a threat in the era of highly active...

...1623-28.
69 Grau I, Pallares R, Tubau F, et al. Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy ...

...40.

70 Heffernan RT, Barrett NL, Gallagher KM, et al. Declining incidence of invasive Streptococcus pneumoniae infections among persons with AIDS in an era of highly active antiretroviral therapy, 1995-2000...

...Jr, Fry AM, et al. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. J Infect Dis 2005; 192: 377-86.

72 Barry PM, Zetola N, Keruly JC, Moore RD, Gebo KA, Lucas GM. Invasive pneumococcal disease in a cohort of HIV-infected adults: incidence and risk factors, 1990-2003. AIDS 2006; 20: 437-44.

73 Kohli R, Lo Y, Homel P, et al. Bacterial pneumonia, HIV therapy, and disease progression among HIV-infected women in the HIV epidemiologic research (HER...

...Le Moing, V, Rabaud C, Journot V, et al. Incidence and risk factors of bacterial pneumonia requiring hospitalization in HIV-infected patients started on a protease inhibitor-containing regimen. HIV Med 2006; 7: 261-67

75 Afessa B, Greaves WL, Frederick WR. Pneumococcal bacteremia in adults: differences between patients with and without human immunodeficiency virus infection. IntJ Infect...

...1997; 2: 21-25.

76 McEllistrem MC, Mendelsohn AB, Pass MA, et al. Recurrent invasive pneumococcal disease in individuals with human immunodeficiency virus infection. J Infect Dis 2002; 185: 1364-68.

77 Turett GS, Blum S, Telzak EE. Recurrent pneumococcal bacteremia: risk factors and outcomes. Arch Intern Med 2001; 161: 2141-44.

78 Nicoletti C, Brandileone MC, Guerra ML, Levin AS. Prevalence, serotypes, and risk factors for pneumococcal carriage among HIV-infected adults. Diagn Microbiol Infect Dis 2007; 57: 259-65.

79 Gebo KA, Moore RD, Keruly JC, Chaisson RE. Risk factors for pneumococcal disease in human immunodeficiency vi rus -infected patients. J Infect Dis 1996; 173: 857-62.

80 Cardoso VC, Cervi MC, Cintra OA, Salathiel AS, Gomes AC. Nasopharyngeal colonization with Streptococcus pneumoniae in children infected with human immunodeficiency virus. J Pediatr (Rio J) 2006; 82: 51-57...

...Spector SA. Decrease in hospitalization and mortality rates among children with perinatally acquired HIV type 1 infection receiving highly active antiretroviral therapy. Clin Infect Dis 2004; 39: 725-31.

83 Dayan PS, Chamberlain JM, Arpadi SM, Farley JJ, Stavola JJ, Rakusan TA. Streptococcus pneumoniae bacteremia in children infected with HIV presentation, course, and outcome. Pediatr Emerg Care 1998; 14: 194-97

84 McGregor D, Barton M, Thomas S, Christie CD. Invasive pneumococcal disease in Jamaican children. Ann Trop Paediatr 2004; 24: 33-40.

85 Krumholz HM, Sande...

...to hospital in Nairobi, Kenya. Lancet 1990; 336: 545 9.

87 Pesola GR, Charles A. Pneumococcal bacteremia with pneumonia. Mortality in acquired immunodeficiency syndrome. Chest 1992; 101: 150-55.

88 Pallares R, Linares J, Vadillo M, et al. Resistance to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. N EnglJ Med 1995; 333:474-80.

89 Hibbs JR, Douglas JM...

...EN. Prevalence of human immunodeficiency virus infection, mortality rate, and serogroup distribution among patients with pneumococcal bacteremia at Denver General Hospital, 1984-1994. Clin Infect Dis 1997; 25: 195-99.

90 Torres JM, Cardenas O, Vasquez A, Schlossberg D. Streptococcus pneumoniae bacteremia in a community hospital. Chest 1998; 113: 387-90.
91 Turett GS, Blum S, Fazal BA, Justman JE, Telzak EE. Penicillin resistance and other predictors of mortality in pneumococcal bacteremia in a population with high human immunodeficiency virus seroprevalence. Clin Infect Dis 1999; 29...

...in hospitalized patients with human immunodeficiency virus: a prospective, cohort study. BMC infect Dis 2001; 1: 13.
93 Robinson KA, Baughman W, Rothrock G, et al. Epidemiology of invasive Streptococcus pneumoniae infections in the United States, 1995-1998: opportunities for prevention in the conjugate vaccine era. JAMA 2001; 285: 1729-35.
94 Trampuz A, Widmer AF, Fluckiger U, Haenggi M, Frei R, Zimmerli W. Changes in the epidemiology of pneumococcal bacteremia in a Swiss university hospital during a 15-year period, 1986-2000. Mayo Clin...

...Campo RE, Campo CE, Peter G, et al. Differences in presentation and outcome of invasive pneumococcal disease among patients with and without HIV infection in the pre-HAART era. AIDS Patient Nosocomial bacterial pneumonia in HIV-infected patients: risk factors for adverse outcome and implications for rational empiric antibiotic...

...34: 9-16,
97 Pedro-Botet ML, Sopena N, Garcia-Cruz A, et al. Streptococcus pneumoniae and Legionella pneumophila pneumonia in HIV-infected patients. Scand J Infect Dis 2007; 39: 122-28.
98 Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I. Clin Infect Dis 2000; 30: 100-21.
99 Crewe-Brown HH, Karstaedt AS, Saunders GL, et al. Streptococcus pneumoniae blood culture isolates from patients with and without human immunodeficiency virus infection: alterations in penicillin...

...Babl FE, Pelton SI, Theodore S, Klein JO. Constancy of distribution of serogroups of invasive pneumococcal isolates among children: experience during 4 decades. Clin Infect Dis 2001; 32: 1155-61.
101 Buie KA, Klugman KP, von Gottberg...
...antibiotic resistance and infection with pediatric serogroups/serotypes, in HIV-infected and uninfected adults with pneumococcal bacteremia. J Infect Dis 2004; 189: 1996-2000.
102 Frankel RE, Virata M, Hardalo C, Altice FL, Friedland G. Invasive pneumococcal disease: clinical features, serotypes, and antimicrobial resistance patterns in cases involving patients with and without...

...103 Fry AM, Facklam RR, Whitney CG, Plikaytis BD, Schuchat A. Multistate evaluation of invasive pneumococcal diseases in adults with human immunodeficiency virus infection: serotype and antimicrobial resistance patterns in the United States. J Infect Dis 2003; 188: 643-52.
104 Prymula R, Peeters P, Chrobok V, et al. Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both Streptococcus pneumoniae and non-typable Haemophilus influenzae: a randomised double-blind efficacy study. Lancet 2006; 367: 740...

...105 Black S, Shinefield H, Fireman B et al. Efficacy, safety, and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000; 19: 187-95.
106 O'Brien KL, Moulton LH, Reid R, et al. Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial. Lancet 2003; 362: 355-61.

107 Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N EnglJ Med 2001; 344: 403-09.
108 Klugman KP...

...SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med 2003; 349: 1341-48.
109 Cutts FT, Zaman SM, Enwere G, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. Lancet 2005; 365: 1139-46.
110 Lucero MG, for the ARIVAC consortium. Effectiveness of an 11-valent pneumococcal conjugate vaccine for preventing radiographically confirmed pneumonia in children under 2 years of age: A randomized, double-blind, placebo-controlled trial in...

...111 Overturf GD. American Academy of Pediatrics. Committee on Infectious Diseases. Technical report: prevention of pneumococcal infections, including the use of pneumococcal conjugate and polysaccharide vaccines and antibiotic prophylaxis. Pediatrics 2000; 106: 367-76.
112 Wise RP, Iskander J, Pratt RD, et al. Postlicensure safety surveillance for 7-valent pneumococcal conjugate vaccine. JAMA 2004; 292: 1702-10.
113 King JC Jr, Vink PE, Farley JJ, et al. Comparison of the safety and immunogenicity of a pneumococcal conjugate with a licensed polysaccharide vaccine in human immunodeficiency virus and non-human immunodeficiency virus-infected...

...M, Parks M, Lichenstein R. Safety and immunogenicity of three doses of a five-valent pneumococcal conjugate vaccine in children younger than two years with and without human immunodeficiency virus infection. Pediatrics...

...115 Nachman S, Kim S, King J, et al. Safety and immunogenicity of a heptavalent pneumococcal conjugate vaccine in infants with human immunodeficiency virus type 1 infection. Pediatrics 2003; 112: 66-73.
116 Abzug MJ, Pelton SI, Song LY, et al. Immunogenicity, safety, and predictors of response after a pneumococcal conjugate and pneumococcal polysaccharide vaccine series in human immunodeficiency virus-infected children receiving highly active antiretroviral therapy. Pediatr...
...Adrian P, Kuwanda L, et al. Long-term immunogenicity and efficacy of a 9-valent conjugate pneumococcal vaccine in human immunodeficient virus infected and non-infected children in the absence of a...

...et al. Randomized trial of the quantitative and functional antibody responses to a 7-valent pneumococcal conjugate vaccine and/or 23-valent polysaccharide vaccine among HIV-infected adults. Vaccine 2001; 20: 545-53.
120 Goetz MB, Feikin DR, Lennox JL, et al. Viral load response to a pneumococcal conjugate vaccine, polysaccharide vaccine or placebo among HIV-infected patients. AIDS 2002; 16: 1421-23.
121 WHO. Recommendations for the production and control of pneumococcal conjugate vaccines. World Health Organ Tech Rep Ser 2005; 927: 64-98. http://www.who.int/biologicals/publications/trs/areas/vaccines/pneumo/en/index.html (accessed Sept 24, 2007).
122 King JC Jr, Vink PE, Chang I, et al. Antibody titers eight months after three doses of a five-valent pneumococcal conjugate vaccine in HIV and non-HIV-infected children less than two years of age. Vaccine...

...L, Cutland C, Holm A, Kayhty H, Klugman KP. Quantitative and qualitative antibody response to pneumococcal conjugate vaccine among African human immunodeficiency virus-infected and uninfected ... Papaevangelou VG, Mostrou GI, Theodoridou MC. Immunogenicity and immunological memory induced by a 7-valent pneumococcal CRM197 conjugate vaccine in symptomatic HIV-I infected children. Vaccine 2005; 23: 5289-93.

125 Tarrago D...

...Ruiz -Contre ras J, et al. Assessment of antibody response elicited by a 7-valent pneumococcal conjugate vaccine in pediatric human immunodeficiency virus infection. Clin Diagn Lab Immunol 2005; 12: 165-70.

126 Madhi SA, Kuwanda L, Cutland C, Klugman KP. The impact of a 9-valent pneumococcal conjugate vaccine on the public health burden of pneumonia in HIV-infected and uninfected children. Clin Infect Dis 2005; 40: 1511-18.

127 Hendley JO, Sande MA, Stewart PM, Gwaltney JM Jr. Spread of Streptococcus pneumoniae in families. I. Carriage rates and distribution of types. J Infect Dis 1975; 132: 55-61.

128 Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease. Active Bacterial Core Surveillance Team. N Engl J Med 2000; 342: 681-89.

129 Hammitt LL, Bruden DL, Butler JC, et al. Indirect effect of conjugate vaccine on adult carriage of Streptococcus pneumoniae : an explanation of trends in invasive pneumococcal disease. J Infect Dis 2006; 193: 1487-94.

130 Kellner JD, Church DL, MacDonald J, Tyrrell GJ, Scheifele D. Progress in the prevention of pneumococcal infection. CMAJ 2005; 173: 1149-51.

131 Kyaw MH, Lynfield R, Schaffner W, et al. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant Streptococcus pneumoniae. N Engl J Med 2006; 354: 1455-63.

132 Rodriguez-Barradas MC, Tharapel RA, Groover JE, et al. Colonization by Streptococcus pneumoniae among human immunodeficiency virus-infected adults: prevalence of antibiotic resistance, impact of immunization, and characterization by polymerase chain reaction with BOX primers of isolates from persistent S pneumoniae carriers. J Infect Dis 1997; 175: 590-97

133 Rusen ID, Fra ser- Roberts L, Slaney L, et al. Nasopharyngeal pneumococcal colonization among Kenyan children: antibiotic resistance, strain types and associations with human immunodeficiency virus type 1 infection. Pediatr Infect Dis J 1997; 16:656-62.

134 Polack FP, Flayhart DC, Zahurak...

...19: 608-12.

135 Flannery B, Heffernan RT, Harrison LH, et al. Changes in invasive pneumococcal disease among HIV-infected adults living in the era of childhood pneumococcal immunization. Ann Intern Med 2006; 144: 1-9.

136 Dagan R, Givon-Lavi N, Zamir O, Fraser D. Effect of a nonavalent conjugate vaccine on carriage of antibiotic-resistant Streptococcus pneumoniae in day-care centers. Pediatr Infect Dis J 2003; 22: 532-40.

137 Mbelle N...

...Kimura A, Chang I, Klugman KP. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. J Infect Dis 1999; 180: 1171-76.

138 Moore MR, Hyde TB, Hennessy TW, et al. Impact of a conjugate vaccine on community- wide carriage of nonsusceptible Streptococcus pneumoniae in Alaska. J Infect Dis 2004; 190: 2031-38.

139 Kaplan SL, Mason EO Jr, Wald ER, et al. Decrease of invasive

pneumococcal infections in children among 8 children's hospitals in the United States after the introduction of the 7-valent pneumococcal conjugate vaccine. Pediatrics 2004; 113: 443-49.
    140 Ray GT, Whitney CG, Fireman BH, Ciuryla V, Black SB. Cost-effectiveness of pneumococcal conjugate vaccine. Evidence from the first 5 years of use in the United States incorporating herd effects. Pediatr Infect Dis J 2006...

...McCann L. Policy analysis of the use of hepatitis B, Haemophilus influenzae type b, Streptococcus pneumoniae-con)ugate and rotavirus vaccines in national immunization schedules. Health Econ 2000; 9: 19-35.
    142 Sinha A, Levine O, Knoll MD, Muhib F, Lieu TA. Cost-effectiveness of pneumococcal conjugate vaccination in the prevention of child mortality: an international economic analysis. Lancet 2007; 369: 389-96.
    143 Tambarello M, Tacconelli E, Cauda R, Ortona L. Secondary Pneumocystis carinii pneumonia prophylaxis with trimethoprim-sulphamethoxazole does not prevent bacterial pneumonia in HIV-infected persons. AIDS 1996; 10: 1603-04.
    144 Buskin SE, Newcomer LM, Koutsky LA, Hooton TM, Spach DH, Hopkins SG. Effect of trimethoprim-sulfamethoxazole as Pneumocystis carinii pneumonia prophylaxis on bacterial illness, Pneumocystis carimi pneumonia, and death in persons with AIDS. J Acquir Immune Defic Syndr Hum Retrovirol 1999; 20...
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14/3,K/24 (Item 2 from file: 457)
DIALOG(R)File 457:The Lancet

0000061825
USE FORMAT 7 OR 9 FOR FULL TEXT
Epidemiological differences among pneumococcal serotypes
Hausdorff, William P; Feikin, Daniel R; Klugman, Keith P
The Lancet Infectious Diseases vol. 5, 2 PP: 83-93 Feb 2005
DOCUMENT TYPE: PERIODICAL; General Information LANGUAGE: English
RECORD TYPE: New; Fulltext
LENGTH: 11 Pages
WORD COUNT: 9780

Epidemiological differences among pneumococcal serotypes
TEXT:
    The bacterial species Streptococcus pneumoniae consists of 90 immunologically distinct serotypes, of which some possess distinct epidemiological properties. Certain serotypes...

...elderly people. Some serotypes seem to be associated with particular disease syndromes, such as complicated pneumonias in children, or with higher rates of hospitalisation in children or mortality in adults, or are consistently responsible for outbreaks in certain populations. Since pneumococcal conjugate vaccines are directed at specific serotypes, national immunisation advisory committees may wish to consider these serotype-specific properties when considering which vaccine formulation to introduce into a national programme.
    Streptococcus pneumoniae, (the pneumococcus) is a major cause of acute otitis media (AOM), pneumonia, bloodstream infections (bacteraemia), and of a particularly virulent form of meningitis. The highest incidence of pneumococcal disease occurs in the first few years of life and again in elderly people. Pneumonia, especially pneumococcal pneumonia, is considered one of the major causes of childhood mortality in developing countries,1 and of adult mortality worldwide.2 The existence of 90 immunologically distinct

serotypes, differing in the chemical compositions of their respective polysaccharide capsules, further complicates simple epidemiological descriptions.3

Current pneumococcal vaccines elicit immune responses to the polysaccharide capsules. The adult vaccine formulation is comprised of...

...seven to 11 of the most prevalent types are chemically linked to carrier proteins. These conjugates activate T cells to provide sufficient immunological help to elicit antibody production, and to stimulate immunological memory. Introduction of a hepta valent pneumococcal conjugate vaccine formulation (PCV7, representing serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) into the US infant-immunisation programme in 2000 has had a major impact on invasive pneumococcal disease (IPD) incidence in young children, as well as in older age groups through herd immunity.4

Many publications detail the serotypes of S pneumoniae isolated from a variety of populations. These have been important in defining the serotype composition of vaccine formulations, and in understanding their relative epidemiological value in different parts of...

...among individual serotypes. The purpose of this paper is to review what is known about serotype-specific properties, and to discuss their potential implications in the era of conjugate pneumococcal

Serotype distribution studies

The 90 pneumococcal serotypes are grouped in 46 serogroups, based on immunological similarities.5 A review of more than 70 studies concluded that ten serogroups accounted for most paediatric invasive disease in each geographic region (continent), with serogroups 1, 6, 14, 19, and 23 among the most prominent in every region.3 The same serogroups, along with serotype 3, also predominated in older children and adults.

These analyses revealed substantial variation in the proportions...
...By contrast, serogroup coverage in each region for the 11-valent (PCVIl, PCV7 plus serotypes 1, 3, 5, and 7F) vaccine formulation has usually been found to be at least 80%. For older children and...

...were lower (30-60%) but also varied by region; coverages averaged 70-80% for PCVIl.3

The prominence of so-called "developing country serotypes" within several industrialised country populations, most notably serotypes 1 and 5, led to the suggestion that developed and developing countries are not useful epidemiological categories for pneumococcal serotype distribution,3 6 though this remains controversial.7

The serotype as a valid unit of analysis

Although the pneumococcal capsular polysaccharide represents an important virulence factor,8 other gene products also contribute to the...

...the capsular serogroup.10 Therefore, it has been an open question as to whether the pneumococcal capsule per se should be considered a useful variable in epidemiological analyses.

To examine this...

...the frequency with which it was isolated from a sterile site. Both studies identified serotypes 1, 4, and 7F as having a high level of invasiveness. Overall, the variation in invasiveness among strains was associated more with the identity of the capsular serotype, rather than with a specific genotype.11,12 This finding is consistent with the findings...

...was unable to identify any difference in invasiveness in three geographically diverse genotypic lineages of serotype I.13 A second study failed to detect any temporal or geographic differences in

invasiveness for several major serotypes.14
Taken together, these analyses provide some justification for using serotype as the unit of analysis of other biological properties of pneumococci. Indeed, there is evidence that individual serotypes can differ in their relative abilities to activate...serotypes may exist in other parts of the world, as some have suggested.12,17
Serotype differences in nasopharyngeal carriage
Certain serotypes commonly account for the majority of nasopharyngeal carriage isolates...

...children.18 These include most of the serotypes represented in PCV7, with the exception of serotype 4, as well as vaccine-related types 6A and 19A, and PCVIl types 3 and 7F. Other serotypes routinely isolated include members of serogroups 10, 11, 13, 15, 33, and 35.14,18-22 Conversely, serotypes 1, 5, and 46 are rarely detected in nasopharyngeal carriage samples, even in populations in which they...

...26 except perhaps during large outbreaks of these serotypes or in certain children with lobar pneumonias.27 The inability to culture specific pneumococcal serotypes from the nasopharynx is presumably a function of their density and duration of colonisation...

...since all invasive serotypes are presumed to be carried, at least transiently, before invasion.27
Serotype differences in antibiotic resistance
Selection of antibiotic-resistant strains is likely to occur in the...

...resistant to antibiotics.19,23-26 These serotypes are largely represented in PCV7, in particular 6B, 9V, 14, 19F, 23F, and the vaccinerelated types 6A and 19A.29 Conversely, serotype 1 remains highly susceptible to antibiotics. Some serotypes (3, 18C, 15A, and members of serogroup 35), however, are routinely detected in carriage studies but nonetheless have remained susceptible to antibiotics,21,22,30,31 at least until the past 2-3 years.32-35 These findings may reflect the observation25 that certain serotypes/serogroups may be carried for longer periods (eg, 6, 14, 19, and 23) than others (eg, 3, 12, and 33). 25 Lastly, it is worth noting that there are some clones of common serotypes - eg, Spanish 23F clone - that are particularly associated with multidrug resistance, indicating that the genotype, as well as the serotype, has a role in antibiotic resistance. Indeed, studies of the clonality of penicillin-resistant pneumococci in the USA suggest that only a few clones make up more than 80% of such strains.3-8
Serotype differences in hospitalisation rates
The incidence of IPD in children under 6 years of age...

...In a departure from this broad pattern, the reported incidence of IPD caused by serotypes 1, 5, and 7F appears comparable in the two regions.39 Since European studies tend to include only hospitalised ...

...cases, a large proportion of which are occult bacteraemias - it has been hypothesised that serotypes 1, 5, and 7F may be disproportionately responsible for disease that requires hospitalisation (compared with other serotypes), and rarely...
...under 2 years of age found only serotypes represented in PCV7 or the closely related 6A.42
To test the ambulatory/hospitalisation hypothesis would require a direct comparison of the contribution...

...IPD done in Santiago, Chile, Lagos and colleagues43 found that 34/221 hospitalised patients (15.4%) had disease caused by serotypes 1

, 5, and 7F, only a slightly greater proportion than that seen with ambulatory patients (20/178 (11.2...

...72 months of age might have substantially altered their findings, since other studies indicate that serotype 1 is disproportionately associated with complicated pneumonias in older children. In addition, different clinical thresholds for taking blood cultures (and thus different...

...in the Chilean and US contexts also make it difficult to clearly interpret these results.

Serotype differences in disease syndromes

Several studies published in the past few years have suggested that...

...fluid than from blood in children and adults, whereas the converse is true for serotypes 1, 4, and 14.44 Unfortunately, variables such as precise age, hospitalisation rates, and antibiotic resistance are often closely associated with one another, as well as with serotype, making it difficult to disentangle the exact contribution of each. For example, younger children are more likely to present with pneumococcal meningitis than are older children, may be more likely than older children to be hospitalised for bacteraemia or pneumonia, and are more likely to show high levels of antibiotic resistance.45-47

With these...

...in mind, it is noteworthy that several studies have noted a high proportion of severe pneumonia cases caused by serotype 1 and, sometimes, serotype 3 (table 1). Intriguingly, a preliminary report suggests that nasopharyngeal carriage of serotypes 1 and 5 may be highly associated with radiographically and clinically more severe childhood pneumonias.27

It should be noted that, for the two studies that provided information on the comparison groups,48, 49 the median ages of patients with "complicated pneumonia" and "empyema" were 18-24 months older than the patients with "uncomplicated pneumonia" or "without empyema", respectively. Heffron8 also cited the common occurrence of type 1 empyemas in the pre-penicillin era, especially in older children.

The picture in adults may be less clear cut. Whereas serotype 3 has long been reported to have a higher casefatality rate compared with other serotypes, 54-59 this has not been observed in all studies.60,61 Conversely, serotype 1 has been reported to have a lower case-fatality rate in adults.54,56,58,60 Additionally, serotypes 1 and 3 have been implicated in two small studies of pneumococcal peritonitis in adults: each comprised 25-50% of the serotypes isolated.62,63 Finally, non-typeable (ie, nonencapsulated) strains of pneumococci seem to rarely cause invasive disease, but have caused sporadic cases64 and outbreaks of conjunctivitis.65-69

Serotype differences by age: children

A number of paediatric studies have suggested that certain serotypes dominate pneumococcal disease within narrow age ranges. In neonates (<28 days old), 20-25% of IPD cases were due to serotype 1 alone,6,70 or serotypes 1 and 5,41 or types 1, 3, and 5,71,72 or types 3 and 7F.41,70,73 In the same studies, these serotypes were detected in less than 5% of children older than neonates but less than 2 years of age.41,70 One report noted a high percentage of serotype 2 meningitis cases in neonates.74 As a consequence of the prominence of serotypes 1, 3, 5, and 7F in the youngest children, some studies have noted that PCV7 serogroups only comprised 40-50...

...isolates in children under 6 months old.40,41,70

Several studies have specifically examined serotype distribution in children aged 6-24 months old, when invasive-disease incidence is highest, and...

...be approximately 12% higher in children under 2 years old, compared with those aged 2-4 years in IPD cases seen at the hospital or among Navajo children.32,79 However...

...more enriched in outpatient bacteraemias without a focus of infection.80,81

The decline in serotype coverage with PCV7 after the age of 2 years, as expressed as percentage of all IPD, is usually accompanied by a rise in the percentage of IPD caused by serotype 1 (and to a lesser extent, serotype 5) 41,70,75,77-79 In the 2-5 -year-old7,41,53,70,77,78 and over 5-yearold age groups,7,41,77,79,82-84 especially in hospital-based surveillance settings, serotype 1 can constitute 15% and 25-50%, respectively, of invasive-disease cases, especially pneumonia.41,70,75,77,79 A similar phenomenon was described by Heffron 60 years ago: in children under 2 years of age and in 2-13-year-olds, serotype 1 accounted for 5 .8% and 26.1% of pneumococcal pneumonias, respectively.8 Some investigators have noted a similar trend for serotype 18C, which comprised 4-9% and 14-25% of isolates from children under 2 years of age and over 2 years old, respectively.46,70,83,85 Figure 1 presents a schematic depiction of serogroup coverage by paediatric age group by PCV7 and by PCV11.

Differences in serotype incidence as a function of age

Thus far, we have discussed the relative percentage of disease caused by one or another serotype. However, the absolute incidence of IPD also changes with age. To better understand the association of serotype with age, we calculated serotype-specific incidence rates by combining population-based incidence figures and serotype distribution percentages for the same population (A von Gottberg and KPK, National Institute for Communicable...

...few years,40,70,83,86 eventually reaching levels in older children that are 2-3% of those seen in the youngest infants. These results are consistent with the hypothesis that...

...to antibody to capsule, contribute to this protection.

The incidence of disease caused by serotypes 1 and 5 together also peaks in the first year of life, mostly due to infection and subsequent...
...next several years. This pattern is apparent in both settings with a high incidence of serotype 1 (eg, Alaskan natives, South Africa, and Israel) and lower incidence settings (eg, USA and western is the mixed picture with 18C, which in one study showed an age-associated pattern similar to other PCV7 types,40 and in three others was like serotypes 1 and 5.70,83,86

When the absolute incidence by serotype is translated into numbers of IPD cases, it becomes apparent that a substantial proportion of ...

...example, of 1123 IPD cases described in children under 7 years of age, 170 (15.1%) occurred in children under 6 months old, and 317 (28%) occurred in children 2-6...

...or Europe, because the current primary series consists of three doses beginning at 2 or 3 months of age and given 1-2 months apart, followed by a booster in the second year of life. However, immunogenicity ...

...programme, despite many children receiving less than the full primary series due to vaccine shortages.4 The US post-marketing surveillance also suggested that a considerable portion of IPD cases occurring outside the 6-24-month age range is preventable by herd immunity.4 Multi-year

surveillance will be needed to assess the duration of protection afforded to older children by previous immunisation as infants.

Serotype differences by age: adults

The proportion of infections caused by the seven "paediatric" serotypes included in PCV7 is lower among adults than children in all geographic regions.3 Nonetheless, PCV7 serotypes constituted 59% of adult invasive disease in the USA in 1998.28 Family transmission of pneumococci from young infants to their susceptible parents and grandparents is the likely mode of transmission...

...to be a significant risk factor for IPD in adults.89 Such intrafamily transmission of pneumococcal serotypes is well described,90 and is being investigated with molecular tools able to discriminate among pneumococcal strains belonging to a single serotype.91 There is some suggestion that transmission from children to adults may be most likely...

...serotypes are more prevalent in elderly adults, as compared with non-elderly adults, particularly types 6B, 14, and 23F .93-96 The reason why elderly people have an increase in infections with these serotypes...
...IPD due to these serotypes has declined considerably in the elderly since the introduction of conjugate vaccine for children.4

HIV-infected adults also tend to have more infections with PCV7 serotypes, as evidenced by...

...continents - Africa and North America (table 2). Several studies showed that the association between paediatric serotype and invasive disease in HIV-infected adults is not due to the increased burden of...

...small studies in the USA have failed to find an increase in the carriage of pneumococci in HIV-infected adults, this has been documented in Africa (28% versus 16%, p=0...

...represent another significant risk group for invasive disease due to PCV7 or related serotypes, including 6B, 9N, 18C, 19F, and 23F (adjusted odds ratio 1.56, 95% CI 1.12-2.18; p=0.008). 98

Serotype differences in replacement after conjugate vaccination

Many clinical studies have shown that receipt of conjugate vaccine is accompanied by a rapid and complete shift, at the level of the nasopharynx...
...accompanied by only a small, statistically insignificant rise in disease caused by non-vaccine types.4 A second, hospitalbased study also reported a large decrease in overall disease, but noted a...one of two PCV7 formulations or a placebo (hepatitis B vaccine). Children who received either conjugate vaccine had fewer pneumococcal AOM cases overall, and fewer AOM cases caused by each of the seven vaccine types compared with the placebo group. By contrast, children who received the conjugate vaccines had more cases of AOM caused by members of serogroups 33, 35, and 38...

...be limited, since the considerable numbers of cases of AOM caused by non-PCV7 serogroups 3 and 22 in the placebo group did not increase in the PCV7-vaccinated groups. It is important to reiterate that, overall, there still was a net decrease of pneumococcal AOM in the PCV7-immunised population.

In a similar vein, the demonstration that a conjugate vaccine formulation had a substantial impact on pneumonia,105 despite evidence of rapid and complete nonvaccine-type replacement in carried strains in the...

...community,24 suggests that non-vaccine types are less able than vaccine types to cause pneumonia.

Serotypes causing pneumococcal outbreaks

Historically, the pneumococcus was a major cause of large, lethal epidemics of pneumonia. In the early part of the 20th century, multiple pneumococcal outbreaks were described among military recruits, prisoners, institutionalised people, and miners.8,111-121 Heffron8 pointed out that serotypes 1, 2, and 5 caused most of these outbreaks. Pharyngeal carriage of the homologous type was increased among people...

...carriage of these three serotypes was rare among healthy individuals in the general community.8

Pneumococcal outbreaks have become rare today. A review of the literature identified 25 pneumococcal outbreaks of IPD in the 1990s, none of which involved more than 35 people.122 It is not clear why pneumococcal outbreaks have become uncommon, but it is likely related to availability of antibiotics and improvements...

...28 By contrast with the pre-antibiotic era outbreaks, the recent outbreaks have a wider serotype distribution, and seem to fall into two epidemiological patterns - outbreaks in the very young and in elderly people, and those in non-elderly adults (table 3).

Outbreaks among the very young and the very old are mostly caused by serotypes that...

...to be frequent colonisers of the nasopharynx, including some of the serotypes in the heptavalent conjugate vaccine (ie, 4, 9V , 14, and 23F) and type 3. Although not included in the table, most small outbreaks in hospitalised patients have also been...

...postulated that viral respiratory infections in a population can predispose it to an outbreak of pneumococcal pneumonia with the predominantly carried strains in that population.111,124-140,141

By contrast, outbreaks...

...elderly adults in homeless shelters, jails, and military settings have mostly been caused by type 1, a leading cause of outbreaks in the pre-antibiotic era. Types 5, 12F, and 8 are, like type 1, rarely carried in children, and have also caused isolated outbreaks in these populations (table 3). Although the sizes of these outbreaks are smaller than those of the past, they share...

...impoverished, communal settings - with the large outbreaks of the past. The persistent propensity of type 1 to cause outbreaks raises the question whether much of the sporadic invasive disease ascribed to type 1 in non-US studies is in fact part of undetected local or community-wide outbreaks.3 Some support for this notion lies in the high variability in the proportion of IPD due to type 1 in contemporaneous studies done in the same country in different sites,3 among distinct populations in one site,7 and in the same population in consecutive years.84,142-143

Conclusion

We examine the epidemiological differences between pneumococcal serotypes beyond their overall prevalence in different parts of the world. Serotypes included in PCV7...

...provide considerably broader and greater protection, even in countries where PCV7 coverage is high. Serotypes 1 and 3, for example, seem to predominate in certain narrow age ranges, such as neonates and older children, to be associated with complicated pneumonia and with peritonitis, and, in the case of serotype 1, to cause outbreaks in adults. There are preliminary suggestions that serotypes 3,

18C, and 15A may be less likely to become antibiotic resistant than would be expected from of disease after conjugate vaccination. However, we do not know whether some of these epidemiological properties should be more properly ascribed to certain genotypic clones, rather than to all clones of a given serotype. Only continued epidemiological and clinical surveillance will reveal some of these answers, but recognising the epidemiological patterns among known pneumococcal serotypes will help us interpret what is found.

Conflicts of interest

WPH is a full-time employee of GlaxoSmithKline Biologicals, which has a pneumococcal conjugate vaccine development programme; DRF reports no conflicts; KPK has received consulting fees, lecture fees, and ...

...from Wyeth and consulting fees from Aventis Pasteur and GlaxoSmithKline Biologicals, each of which have pneumococcal conjugate vaccine development programmes.

Acknowledgments

We thank Bin Zou for statistical assistance, and R Dagan, D...

...A von Gottberg, and C Whitney for providing unpublished incidence data.

Lancet Infect Dis 2005; 5: 83-93

WPH is the director of epidemiology, GlaxoSmithKline Biologicals, King of Prussia, PA, USA...

SIDEBAR:

...well as the searches of the extensive files of the authors. Primary search terms included "serotype" or "serogroup" and "pneumococcus" or "Streptococcus pneumoniae". Although the primary focus of the review was on studies published in the past 5-7 years, in some cases we examined selected studies and reviews from the older medical...

CITED REFERENCES:

References

1 Williams BG, Gouws E, Boschi-Pinto C, Bryce J, Dye C. Estimates of world-wide...

...Lancet Infect Dis 2002; 2: 25-32.

2 Fedson DS, Scott JAG. The burden of pneumococcal disease among adults in developed and developing countries: what is and is not known. Vaccine 1999; 17 (suppl 1): S11-18.

3 Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I. Clin Infect Dis 2000; 30: 100-21.

4 Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med 2003; 348:1737-46.

5 Henrichsen J. Six newly recognized types of Streptococcus pneumoniae. J Clin Microbiol 1995; 33: 2759-62.

6 Sleeman K, Knox K, George R, et al. Invasive pneumococcal disease in England and Wales: vaccination implications. J Infect Dis 2001; 183: 239-46.

7...

...D, Givon-Lavi N, Bilenko N, Dagan R. A decade (1989-1998) of pediatric invasive pneumococcal disease in 2 populations residing in 1 geographic location: implications for vaccine choice. Clin Infect Dis 2001; 33: 421-27.

8 Heffron R. Pneumonia with special reference to pneumococcus lobar pneumonia. The Commonwealth Fund: New York, 1939.

9 Hollingshead SK, Briles DE. Streptococcus pneumoniae: new tools for an old pathogen. Curr Opin Microbiol 2001; 4: 71-77.

10 Taha MK, Deghmane AE, Antignac A, Zarantonelli ML, Larribe M, Alonso

JM...

...Meats E, Peto T, Crook DW, Spratt BG. Clonal relationships between invasive and carriage Streptococcus pneumoniae and serotype- and clone-specific differences in invasive disease potential. J Infect Dis 2003; 187: 1424-32...

...Effect of clonal and s ero type- specific properties on the invasive capacity of Streptococcus pneumoniae. J Infect Dis 2004; 189: 785-96.

13 Brueggemann AB, Spratt BG. Geographic distribution and clonal diversity of Streptococcus pneumoniae serotype 1 isolates. J Clin Microbiol 2003; 41:4966-70.

14 Brueggemann AB, Peto TEA, Crook DW, Butler JC, Kristinsson KG, Spratt BG. Temporal and geographic stability of the serogroupspecific invasive disease protential of Streptococcus pneumoniae in children. J Infect Dis 2004; 190: 1203-11.

15 Fedson DS, Musher DM, Eskola J. Pneumococcal vaccine. In: Plotkin SA, Orenstein WA, eds. Vaccines. Philadelphia, USA: WB Saunders Company, 1999.

16 Austrian R. Epidemiology of pneumococcal capsular types causing pediatric infections. Ped Infect Dis J 1989; 8 (suppl): S21-22.

17...

...Lu CY, Lee PI, Lee CY, Huang LM. Clinical manifestations and molecular epidemiology of necrotizing pneumonia and empyema caused by Streptococcus pneumoniae in children in Taiwan. Clin Infect Dis 2004; 38: 830-35.

18 Bogaert D, De Groot R, Hermans PW. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. Lancet Infect Dis 2004; 4: 144-54.

19 Feikin DR, Davis M, Nwanyanwu OC, et al. Antibiotic resistance and serotype distribution of Streptococcus pneumoniae colonizing rural Malawian children. Pediatr Infect Dis J 2003; 22: 564-67.

20 Rusen ID, F ras er- Roberts L, Slaney L, et al. Nasopharyngeal pneumococcal colonization among Kenyan children: antibiotic resistance, strain types and associations with human immunodeficiency virus type 1 infection. Pediatr Infect Dis J 1997; 16:656-62.

21 Syrogiannopoulos GA, Katopodis GD, Grivea IN, Beratis NG. Antimicrobial use and serotype distribution of nasopharyngeal Streptococcus pneumoniae isolates recovered from Greek children younger than 2 years old. Clin Infect Dis 2002; 35...

...82.

22 Yagupsky P, Porat N, Fraser D, et al. Acquisition, carriage, and transmission of pneumococci with decreased antibiotic susceptibility in young children attending a day care facility in southern Israel...

...Cherian T, Raghupathy P, et al. Nasopharyngeal colonization of infants in southern India with Streptococcus pneumoniae. Epidemiol Infect 1999; 123: 383-88.

24 Mbelle N, Huebner RE, Wasas AD, Kimura A, Chang I, Klugman KP. Immunogenicity and impact of nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. J Infect Dis 1999; 180: 1171-76.

25 Smith T, Lehmann D, Montgomery J, Gratten M, Riley ID, Alpers MP. Acquisition and invasiveness of different serotypes of Streptococcus pneumoniae in young children. Epidemiol infect 1993; 111:27-39.

26 Scott JA, Hall AJ, Hannington A, et al. Serotype distribution and prevalence of resistance to benzylpenicillin in three representative populations of Streptococcus pneumoniae isolates from the coast of Kenya. Clin Infect Dis 1998; 27: 1442-50.

27 Dagan R, Givon-Lavi N, Bar-Ziv J, Porat N. The association of nasopharyngeal (NP) S. pneumoniae (Pnc) serotypes with

community-acquired alveolar pneumonia (CAAP) determined by WHO standardization of interpretation of chest radiographs in children (WHO-SICR). 4th International Symposium on Pneumococci and Pneumococcal Diseases; Helsinki, Finland; May 9-13, 2004. Abstract 44.

28 Feikin DR, Klugman KP. Historical changes in pneumococcal serogroup distribution: implications for the era of pneumococcal conjugate vaccines. Clin Infect Dis 2002; 35: 547-55.

29 Whitney CG, Farley MM, Hadler J, et al. Increasing prevalence of multidrug-resistant Streptococcus pneumoniae in the United States. N Eng J Med 2000; 343: 1917-24.

30 Hsueh PR, Luh KT. Antimicrobial resistance in Streptococcus pneumoniae, Taiwan. Emerg Infect Dis 2002; 8: 1487-91.

31 Muhlemann K, Matter HC, Tauber MG, Bodmer T. Nationwide surveillance of nasopharyngeal Streptococcus pneumoniae isolates from children with respiratory infection, Switzerland, 1998-1999. J Infect Dis 2003; 187: 589...

...Kaplan SL, Mason EO Jr, Wald E, et al. Six year multicenter surveillance of invasive pneumococcal infections in children. Pediatr Infect Dis J 2002; 21: 141-47.

33 Gertz RE Jr, McEllistrern MC, Boxrud DJ, et al. Clonal distribution of invasive pneumococcal isolates from children and selected adults in the United States prior to 7-valent conjugate vaccine introduction. J Clin Microbiol 2003; 41: 4194-216.

34 Perez -Traile ro E, Marimon JM, Iglesias L, Larruskain J. Fluoroquinolone and macrolide treatment failure in pneumococcal pneumonia and selection of multidrug-resistant isolates. Emerg Infect Dis 2003; 9: 1159-62.

35 Porat N, Barkai G, Jacobs MR, Trefler R, Dagan R. Four antibioticresistant Streptococcus pneumoniae clones unrelated to the pneumococcal conjugate vaccine serotypes, including 2 new serotypes, causing acute otitis media in southern Israel. J Infect...

...A, Severina EP, Petruk VF, Mauriz YR, Tomasz A. Molecular characterization of penicillin-resistant Streptococcus pneumoniae isolates causing respiratory disease in the Linited States. Microb Drug Resist 1998; 4: 325-37.

37 Gherardi G, Whitney CG, Facklam RR, Beali B. Major related sets of antibiotic-resistant pneumococci in the United States as determined by pulsed-field gel electrophoresis and pbpla-pbp2bpbp2x-dhf...

...SS, LI eilmann KP, Coffman SL, et al. The molecular epidemiology of penicillin-resistant Streptococcus pneumoniae in the United States, 1994-2000. Clin Infect Dis 2002; 34: 330-39.

39 Hausdorff WP, Siber G, Paradiso PR. Geographical differences in invasive pneumococcal disease rates and serotype frequency in young children. Lancet 2001; 357: 950-52.

40 Miller E, Waight P, Efstratiou A, Brisson M, Johnson A, George R. Epidemiology of invasive and other pneumococcal disease in children in England and Wales 1996-1998. Acta Paediatr Suppl 2000; 89: 11...

...Kries R, Hermann M, Hachmeister A, et al. Prediction of the potential benefit of different pneumococcal conjugate vaccines on invasive pneumococcal disease in German children. Pediatr Infect Dis J 2002; 21: 1017-23.

42 Alpern ER, Alessandrini EA, McGowan GL, Bell LM, Shaw KN. Serotype prevalence of occult pneumococcal bacteremia. Pediatrics 2001; 108: E23.

43 Lagos R, Munoz A, Valenzuela MT, Heitmann I, Levine MM. Population-based surveillance for hospitalized and ambulatory pediatric invasive pneumococcal disease in Santiago, Chile. Pediatr Infect Dis J 2002; 21: 1115-23.

44 Hausdorff WP, Bryant J, Kloek C, Paradiso PR, Siber GR. The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use, part II. Clin Infect Dis 2000; 30: 122-40.
45 Dagan...

...N, Shkolnik L, Yagupsky P, Fraser D. Acute otitis media caused by antibiotic-resistant Streptococcus pneumoniae in southern Israel: implication for immunizing with conjugate vaccines. J Infect Dis 2000; 181: 1322-29.
46 Doit C, Loukil C, Geslin P, Bingen E. Phenotypic and genetic diversity of invasive pneumococcal isolates recovered from French children. J Clin Microbiol 2002; 40: 2994-98.
47 LIausdorff WP, Yothers G, Dagan R, et al. Multinational study of pneumococcal serotypes causing acute otitis media in children. Pediatr Infect Dis J 2002; 21: 1008-16...

...Tan TQ, Mason EO Jr, WaId ER, et al. Clinical characteristics of children with complicated pneumonia caused by Streptococcus pneumoniae. Pediatrics 2002; 110: 1-6.
49 Byington CL, Spencer LY, Johnson TA, et al. An epidemiological investigation of a...

...et al. Culture -nega ti ve childhood empyema is usually due to penicillin-sensitive Streptococcus pneumoniae capsular serotype 1. J Clin Microbiol 2003; 41:521-22.
52 Hardie W, Bokulic R, Garcia VF, Reising SF, Christie CDC. Pneumococcal pleural empyemas in children. Clin Infect Dis 1996; 22: 1057-63.
53 Camou T, Palacio R, Di Fabio JL, Hortal M. Invasive pneumococcal diseases in Uruguayan children: comparison between serotype distribution and conjugate vaccine formulations. Vaccine 2003; 21: 2093-96.
54 Austrian R, Gold J. Pneumococcal bacteremia with especial reference to bacteremic pneumococcal pneumonia. Ann Intern Med 1964; 60: 759-76.
55 Gransden WR, Eykyn SJ, Phillips I. Pneumococcal bacteraemia: 325 episodes diagnosed at St. Thomas's Hospital. BMJ 1985; 290: 505-08.
56 Henriques B, Kalin M, Ortqvist A, et al. Molecular epidemiology of Streptococcus pneumoniae causing invasive disease in 5 countries. J Infect Dis 2000; 182: 833-39.
57 Kuikka A, Syrjanen J, Renkonen OV, Valtonen V. Pneumococcal bacteraemia during a recent decade. J Infect 1992; 24: 157-68.
58 Martens P, Worm SW, Lundgren B, Konradsen HB, Benfield T. Serotype-specific mortality from invasive Streptoccus pneumoniae disease revisited. BMC Infect Dis 2004; 4: 21.
59 Ostergaard C, Brandt C, Konradsen LIB, Samuelsson S. Differences in survival, brain damage, and cerebrospinal fluid cytokine kinetics due to meningitis casued by 3 different Streptoccus pneumoniae serotypes: evaluation in hurnans and in 2 experimental models . J Infect Dis 2004; 190: 1212-20.
60 McKenzie H, Reid N, Dijkhuizen RS. Clinical and microbiological epidemiology of Streptococcus pneumoniae bacteraemia. J Med Microbiol 2000; 49: 361-66.
61 Balakrishnan I, Crook P, Morris R, Gillespie SLL Early predictors of mortality in pneumococcal bacteraemia. J. Infect 2000; 40: 256-61.
62 Hemsley C, Eykyn SJ. Pneumococcal peritonitis in previously healthy adults: case report and review. Clin Infect Dis 1998; 27: 376...

...63 Nielsen KR, Ejlertsen T, El-Batran S, Prag J. A five-year survey of pneumococcal peritonitis in two Danish counties-incidence, diagnosis and clinical entities. Clin Microbiol Infect 2003; 9...
...64 Barker JH, Musher DM, Silberman R, Phan HM, Watson DA. Genetic

relatedness among nontypeable pneumococci implicated in sporadic cases of conjunctivitis. J Clin Microbiol 1999; 37: 4039-41.
65 Centers for Disease Control and Prevention. Pneumococcal conjunctivitis at an elementary school - Maine, September 20 December 6, 2002. MMWR Morb Mortal WkIy...

...et al. BOXpolyrnerase chain reaction-based DNA analysis of non s ero type able Streptococcus pneumoniae implicated in outbreaks of conjunctivitis. J Infect Dis 1997; 176: 1401-05.
67 Martin M, Turco JH, Zegans ME, et al. An outbreak of conjunctivitis due to atypical Streptococcus pneumoniae. N Engl J Med 2003; 348: 1112-21.
68 Shayegani M, Parsons LM, Gibbons WE Jr, Campbell D. Characterization of nontypable Streptococcus pneumoniae-like organisms isolated from outbreaks of conjunctivitis. J Clin Microbiol 1982; 16: 8-14.
69 Crurn NF, Barrozo CP, Chapman FA, Ryan MA, Russell KL. An outbreak of conjunctivitis due to a novel unencapsulated Streptococcus pneumoniae among military trainees. Clin Infect Dis 2004; 39: 1148-54.
70 Kaltoft MS, Zeuthen N, Konradsen HB. Epidemiology of invasive pneumococcal infections in children aged 0-6 years in Denmark: a 19-year nationwide surveillance study. Acta Paediatr Suppl 2000; 89: 3-10.
71 Hoffman JA, Mason EO, Schutze GE, et al. Streptococcus pneumoniae infections in the neonate. Pediatrics 2003; 112: 1095-102.
72 Tapia-Morquecho LG, Aguilar-Ituarte F, Gomez-Barreto D, Munguia-De Sierra MT. Sepsis neonatal por Streptococcus pneumoniae serotipo. Bol Med Hosp Infant Mex 2001; 57: 212-16.
73 Gomez M, Alter S, Kumar ML, Murphy S, Rathore MH. Neonatal Streptococcus pneumoniae infection: case reports and review of the literature. Ped Infect Dis J 1999; 18: 1014...

...Brandileone MC, de Andrade AL, Di Fabio JL, Guerra ML, Austrian R. Appropriateness of a pneumococcal conjugate vaccine in Brazil: potential impact of age and clinical diagnosis, with emphasis on meningitis. J Infect Dis 2003; 187: 1206-12.
76 Hausdorff WP. Invasive pneumococcal disease in children: geographic and temporal variations in incidence and serotype distribution. Eur J Pediatr 2002; 161 (suppl): S135-39.
77 Zissis NP, Syriopoulou V, Kafetzis D, et al. Serotype distribution and antimicrobial susceptibility of Streptococcus pneumoniae causing invasive infections and acute otitis media in children. Eur J Pediatr 2004; 163: 364...

...the Portuguese Surveillance Group for the Study of Respiratory Pathogens, Melo-Cristino J. Invasive Streptococcus pneumoniae from Portugal: implications for vaccination and antimicrobial therapy. Clin Microbiol Infect 2004; 10:652-56.
79 O'Brien KL, Shaw J, Weatherholtz R, et al. Epidemiology of invasive Streptococcus pneumoniae among Navajo children in the era before use of conjugate pneumococcal vaccines, 1989-1996. Am J Epidemiol 2004; 160: 270-78.
80 Robinson KA, Baughman W, Rothrock G, et al. Epidemiology of invasive Streptococcus pneumoniae infections in the United States, 1995-1998. Opportunities for prevention in the conjugate vaccine era. JAMA 2001; 285: 1729-35.
81 Centers for Dieseae Control and Prevention. Preventing pneumococcal disease among infants and young children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mort Wk Rep 2000; 49: RR-9.
82 Ramdani-Bouguessa N, Rahal K. Serotype distribution and antimicrobial resistance of Streptococcus pneumoniae isolated in

Algiers, Algeria. Antimicrob Agents Chemother 2003; 47: 824-26.
83 Paragi M, Kolman J, Kraigher A, et al. Possibility of application of new pneumococcal conjugate vaccines in children in Slovenia. Vaccine 2003; 21: 4708-14.
84 Hedlund J, Sorberg M, Henriques Normark B, Kronvall G. Capsular types and antibiotic susceptibility of invasive Streptococcus pneumoniae among children in Sweden. Scand J Infect Dis 2003; 35: 452-58.
85 Fenoll A, Jado I, Vicioso D, Berron S, Yuste JE, Casal J. Streptococcus pneumoniae in children in Spain: 1990-1999. Acta Paediatr Suppl 2000; 89: 44-50.
86 Rudolph KM, Parkinson AJ, Reasonover AL, Bulkow LR, Parks DJ, Butler JC. Serotype distribution and antimicrobial resistance patterns of invasive isolates of Streptococcus pneumoniae: Alaska, 1991-1998. J Infect Dis 2000; 182: 490-96.
87 Goldblatt D, Ashton L, Southern J, et al. Immunogenicity and boosting following a reduced number of doses of a pneumococcal conjugate vaccine in infants and toddlers. Programme and Abstracts of 4th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD-4 2004); Helsinki, Finland; May 9-13, 2004. Abstract NEW-06.
88 Pilishvili T, Farley M, Vazquez M, et al. Effectiveness of heptavalent pneumococccal conjugate vaccine in children. Abstracts of 43rd Interscience Conference on Antimicrobial Agents and Chemotherapy; Chicago, IL, USA; Sept 14-17, 2003. Abstract G-1079.
89 Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease. N Engl J Med 2000; 342: 681-89.
90 Gwaltney JM Jr, Sande MA, Austrian R, Hendley JO. Spread of Streptococcus pneumoniae in families. II. Relation of transfer of S. pneumoniae to incidence of colds and serum antibody. J Infect Dis 1975; 132: 62-68.
91 Regev-Yochay G, Raz M, Dagan R, et al. Nasopharyngeal carriage of Streptococcus pneumoniae by adults and children in community and family settings. Clin Infect Dis 2004; 38: 632...

...K, Watanabe H, Sugita R, et al. High rate of transmission of penicillin-resistant Streptococcus pneumoniae between parents and children. J Clin Micro 2002; 40: 4357-59.
93 Colman G, Cooke EM, Cookson BD, Cooper PG, Efstratiou A, George RC. Pneumococci causing invasive disease in Britain 1982-1990. J Med Microbiol 1998; 47: 17-27.
94 Kyaw MH, Christie P, Clarke SC, et al. Invasive pneumococcal disease in Scotland, 1999-2001: use of record linkage to explore associations between patients and...

...Svenson SB, Kalin M, et al. Incidence, capsular types, and antibiotic susceptibility of invasive Streptococcus pneumoniae in Sweden. Clin Infect Dis 1995; 21: 948-53.
96 Scott JAG, Hall AJ, Dagan R, et al. Serogroup-specific epidemiology of Streptococcus pneumoniae: associations with age, sex, and geography in 7,000 episodes of invasive disease. Clin Infect...

...EN. Prevalence of human immunodeficiency virus infection, mortality rate, and serogroup distribution among patients with pneumococcal bacteremia at Denver General Hospital, 1984-1994. Clin Infect Dis 1997; 25: 195-99.
98 Fry AM, Facklam RR, Whitney CG, Plikaytis BD, Schuchat A. Multistate evaluation of invasive pneumococcal diseases in adults with human immunodeficiency virus infection: serotype and antimicrobial resistance patterns in the United States. J ...Brown HH, Karstaedt AS, Saunders GL, Khoosal M, Jones N, Wasas A, Klugman KP. Streptococcus pneumoniae blood culture isolates from patients with and without human immunodeficiency virus infection: alterations in penicillin...

...Huebner R, Khoosal M, Crewe-Brown LI, Klugman K. The impact of HIV on Streptococcus pneumoniae bacteraemia in a South African population. AIDS 1998; 12: 2177-84.
101 Buie KA, Klugman...
...for antibiotic resistance and infection with pediatric serogroups in HIV-infected and uninfected adults with pneumococcal bacteremia. J Infect Dis 2004; 189: 1996-2000.
102 Paul J. Royal Society of Tropical Medicine and Hygiene meeting at Mansion House, London, December 12, 1996. H IV and pneumococcal infection in Africa. Microbiological aspects. Trans R Soc Trop Med Hyg 1997; 91: 632-37.
103 Klugman KP. Efficacy of pneumococcal conjugate vaccines and their effect on carriage and antimicrobial resistance. Lancet Infect Dis 2001; 1: 85-91.
104 Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000; 19: 187-95.
105 Klugman KP, Madhi SA, Huebner RE, et al. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. N Engl J Med 2003; 349...

...O'Brien KL, Moulton LH, Reid R, et al. Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: group randomised trial. Lancet 2003; 362: 355-61.
107 Kaplan SL, Mason EO Jr, WaId ER, et al. Decrease of invasive pneumococcal infections in children among 8 children's hospitals in the United States after the introduction of the 7-valent pneumococcal conjugate vaccine. Pediatrics 2004; 113:443-49.
108 Schuchat A, Flannery B, Heffernan R, et al. Invasive pneumococcal disease in HIV-AIDS: Has introduction of 7-valent pneumococcal conjugate vaccine (PCV-7) reduced HIV-related disease burden in the US? 4th International Symposium on Pneumococci and Pneumococcal Diseases; Helsinki, Finland; May 9-13, 2004. Abstract EPI-05.
109 Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 2001; 344: 403-09.
110 Kilpi T, Ahrnan LI, Jokinen J, et al. Efficacy of a second pneumococcal conjugate vaccine against pneumococcal acute otitis media in infants and children: randomized, controlled trial of a 7-valent pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine in 1666 children. Clin Infect Dis 2003; 37: 1155-64.
111 Hodges RG, MaCleod CM. Epidemic pneumococcal pneumonia: V. Final consideration of the factors underlying the epidemic. Am J Hyg 1946; 44: 237-43.
112 Lister S, Ordman D. Epidemiology of pneumonia on the Witwatersrand goldfields and prevention of pneumonia an other allied acute respiratory disease in native labourers in south Africa by means of vaccine. Publ South African Inst Med Res 1935; 7: 1-81.
113 Macleod CM, Hodges RG, Heidelberger M, Bernhard WG. Prevention of pneumococcal pneumonia by immunization with specific polysaccharides. J Exp Med 1945; 82: 445-65.
114 Nichols HJ. Lobar pneumonia problem in the army from viewpoint of the recent differentiation of types of pneumococci. Mil Surgeon 1917; 41: 149-61.
115 Ordman D. Pneumonia in native mine workers of the Witwatersrand goldfields. A bacterilocial and epidemilocial study. J Med Assoc South Africa 1931; 5: 108-16.
116 Schroder MC, Cooper G. An epidemic of colds, bronchitis and pneumonia due to type V pneumococci. J Infect Dis 1930; 46: 384-92.

117 Smillie WG. A study of an outbreak of type II pneumococcus pneumonia in the Veterans Administration Hospital at Bedford, Massachusetts. Am J Hyg 1936; 24: 522-35.
118 Smillie WG, Warnock GH, White HJ. A study of a type II pneumococcus epidemic at the state hospital at Worcester, Mass. Am J Public Health 1938; 28: 293-302.
119 Stillman EG. Further studies on the epidemiology of lobar pneumonia. J Exper Med 1917; 26: 513-35.
120 Strom A. Epidemic of croupous pneumonia caused by pneumococcus type 1. J Infect Dis 1932; 50: 430-6.
121 Sydenstricker VPW, Sutton AC. Epidemiological study of lobar pneumonia. Bull Johns Hopkins Hosp 1917; 28: 312-5.
122 Gleich S, Morad Y, Echague R, et al. Streptococcus pneumoniae serotype 4 outbreak in a home for the aged: report and review of recent outbreaks. Infect Control...

...123 Quick RE, Hoge CW, Hamilton DJ, Whitney CJ, Borges M, Kobayashi JM. Underutilization of pneumococcal vaccine in nursing homes in Washington State: report of a serotype-specific outbreak and a survey. Am J Med 1993; 94: 149-52.
124 Fiore AE, Iverson C, Messmer T, et al. Outbreak of pneumonia in a long-term care facility: Antecedent human parainfluenza virus 1 infection may predispose to bacterial pneumonia. J Am Geriatr Soc 1998; 46: 1112-17.
125 Centers for Disease Control and Prevention. Outbreaks of pneumococcal pneumonia among unvaccinated residents in chronic-care facilities - Massachusetts, October 1995, Oklahoma, February 1996, and Maryland...

...62.
126 Nuorti JP, Butler JC, Crutcher JM, et al. An outbreak of multidrug-resistant pneumococcal pneumonia and bacteremia among unvaccinated nursing home residents. N Engl J Med 1998; 338: 1861-68.
127 Sheppard DC, Bartlett KA, Lampiris HW. Streptococcus pneumoniae transmission in chronic-care facilities: description of an outbreak and review of management strategies. Infect...

...Hosp Epidemiol 1998; 19: 851-53.
128 Centers for Disease Control and Prevention. Outbreak of pneumococcal pneumonia among unvaccinated residents of a nursing home - New Jersey, April 2001. MMWR Morb Mortal Wkly...

...50: 707-10.
129 Besees JG, Ugarriza AV, Sancho CA, et al. Transmision de Streptococcus pneumoniae en una residencia de ancianos: analisis de un brote epidemico. Med Clin (Barc) 2003; 121 R, Pickering LK. Invasive disease due to multiply resistant Streptococcus pneumoniae in a Houston, Tex, Day-care center. Am J Dis Child 1990; 144: 923-27...

...T, Steinhoff MC, Harrison LH, Rohn D, McDougal LK, Dick J. A cluster of invasive pneumococcal disease in young children in child care. JAMA 1994; 271: 695-97.
132 Craig AS, Erwin PC, Schaffner W, et al. Carriage of multidrug-resistant Streptococcus pneumoniae and impact of chemoprophylaxis during an outbreak of meningitis at a day care center. Clin...

...133 Mufson MA, Kruss DM, Wasil RE, Metzger WI. Capsular types and outcomes of bacterernic pneumococcal disease in the antibiotic era. Arch Intern Med 1974; 134: 505-10.
134 DeMaria A Jr, Browne K, Berk Sl, Sherwood EJ, McCabe WR. An outbreak of type 1 pneumococcal pneumonia in a men's shelter. JAMA 1980; 244: 1446-49.

135 Mercat A, Nguyen J, Dautzenberg B. An outbreak of pneumococcal pneumonia in two men's shelters. Chest 1991; 99: 147-51.
136 Hoge CW, Reichler MR, Dominguez EA, et al. An epidemic of pneumococcal disease in an overcrowded, inadequately ventilated jail. N Engl J Med 1994; 331: 643-48.
137 Gratten M, Morey F, Dixon J, et al. An outbreak of serotype 1 Streptococcus pneumoniae infection in central Australia. Med J Aust 1993; 158: 340-42.
138 Dagan R, Gradstein S, Belmaker I, et al. An outbreak of Streptococus pneumoniae serotype 1 in a closed community in southern Israel. Clin Infect Dis 2000; 30: 319-21.
139 Proulx JF, Dery S, Jette LP, Ismael J, Libman M, De Wals P. Pneumonia epidemic caused by a virulent strain of Streptococcus pneumoniae serotype 1 in Nunavik, Quebec. Can Commun Dis Rep 2002; 28: 129-31.
140 Crum NF, Wallace MR, Lamb CR, et al. Halting a pneumococcal pneumonia outbreak among United States Marine Corps trainees. Am J Prev Med 2003; 25: 107-11...

...PE, Musher DM, Glezen WP, Rodriguez-Barradas MC, Nahm WK, Wright CE. Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution, and the isolation of respiratory viruses. Clin Infect Dis 1996; 22: 100-06.
142 Konradsen HB, Kaltoft MS. Pneumococcal infections in Denmark from 1995 to 1999: epidemiology, serotypes, and resistance. Clin Diagn Lab Immun...

...65.
143 Pedersen MK, Hoiby EA, Froholm LO, Hasseltvedt V, Lermark G, Caugant DA. Systemic pneumococcal disease in Norway 1995-2001: capsular types and antimicrobial resistance. Epidemiol Infect 2004; 132: 167...
THIS IS THE FULL-TEXT.

14/3,K/25 (Item 3 from file: 457)
DIALOG(R)File 457:The Lancet

0000059786
USE FORMAT 7 OR 9 FOR FULL TEXT
Incidence of macrolide resistance in Streptococcus pneumoniae after introduction of the pneumococcal conjugate vaccine: population-based assessment
Stephens, David S; Zughaier, Susu M; Whitney, Cynthia G; Baughman, Wendy S; Et al
Georgia Emerging Infections Program
The Lancet vol. 365, 9462 PP: 855-63 Mar 5-Mar 11, 2005
DOCUMENT TYPE: PERIODICAL; Journal Article LANGUAGE: English
RECORD TYPE: New; Fulltext
LENGTH: 9 Pages
WORD COUNT: 5821

TEXT:
...pneumococcal disease and macrolide resistance were striking in African-Americans after introduction of the pneumococcal conjugate vaccine, an effective strategy for reducing the burden of disease and resistance in this high...

...due to high density households in urban Atlanta or focused targeting in African-Americans 2-4 years of age in the vaccine catch-up schedule, are possibilities to be investigated.

The decline in overall macrolide resistance was the result of the decrease in incidence of pneumococcal disease due to the vaccine serogroups frequently associated with macrolide and other antibiotic resistance (eg, mefE in serotype 14). Declines in resistance to penicillin, other beta-lactam antibiotics, and to other antibiotics have also...

...not find evidence for a slowing of the spread of mefE-associated macrolide resistance among pneumococci. The rate of macrolide resistance in serotype-14 isolates was 78% in 2002, the rate of macrolide resistance in 19A isolates increased, and there were significant increases in the incidence of mefE resistance in invasive S pneumonias of non-vaccine serotypes. These data suggest that the selective pressure for macrolide resistance continues in our population and that the beneficial effect of the pneumococcal conjugate vaccine on macrolide resistance might be short-lived if concurrent measures to promote appropriate antibiotic use are ignored. In Atlanta up to 2002, serotype replacement with non-vaccine serotypes as a cause of invasive pneumococcal disease was not seen. However, trends in the incidence and macrolide resistance of certain serotypes (19A, 33F) are of concern and serotype replacement has been reported in other settings.

The decline in invasive pneumococcal disease and macrolide resistance occurred despite substantial shortages of pneumococcal conjugate vaccine. Between August, 2001, and May, 2003, shortages affected coverage of children.14 As in Atlanta (figure 2), in the whole USA only 37% of children in birth...

...restrictions in coverage, the impressive declines in adult cases who were not vaccinated with the conjugate vaccine indicate a large herd immunity effect of the pneumococcal conjugate vaccine. Significant herd immunity effects were also seen in a South African study with a pneumococcal conjugate vaccine,29 and the vaccines decrease rates of pneumococcal pneumonia and otitis media caused by vaccine serotypes.28-30 Continued surveillance will be necessary to monitor future trends in pneumococcal-disease incidence and the long-term effects on antibiotic resistance.

The substantial rise in erythromycin resistance due to efflux in S pneumoniae and the subsequent fall paralleling the introduction of the heptavalent pneumococcal conjugate vaccine show both the rapid selection and spread of an antibiotic resistance determinant in pneumococci and the opportunity for effective vaccines that effect transmission to reduce rates of disease and...

...We thank the Georgia Emerging Infections Program staff, hospitals, and laboratories in Georgia Health District 3 for their continued contributions to the project; Lane Pucko for editorial assistance; Grace Beshara, Whitney...

SIDEBAR:

CAPTIONS:

Figure 1: Incidence of invasive S pneumoniae in metropolitan Atlanta, 1994-2002

Table 1: Incidence of invasive pneumococcal disease in metropolitan Atlanta by year, age-group, macrolide resistance, and mechanism of resistance

Figure 2: Pneumococcal conjugate vaccine coverage in Atlanta, 2000-2003

Percentage of children aged 19-35 months in two central metropolitan Atlanta counties (Fulton and DeKalb) of HD-3 who had received at least one, two, three, or four doses of the vaccine. Data are expressed by quarter of 2000, 2001, 2002, and the first half of 2003.

Figures. 3 Incidence of invasive S pneumonioe disease by age-group, in metropolitan Atlanta 1994-2002

Table 2: MIC to erythromycin of mefE-containing S pneumoniae, metropolitan Atlanta, 1995-2002
Figure 4: Distribution of invasive S pnewnoniae by serotype
Numbers inside each pie section represent number of cases caused by the serotype listed outside the pie chart; designated serotypes include the seven serotypes in the heptavalent conjugate vaccine, plus vaccine-related serotypes 6A and 19A; "others" refers to non-conjugate vaccine serotypes.
Table 3: Incidence of invasive pneumococcal disease in metropolitan Atlanta by year, serotype, macrolide resistance, and mechanism of resistance
Table 4: Incidence of macrolide resistance in pneumococcal serotype 14 isolates by year and age-group
CITED REFERENCES:

14/3,K/26 (Item 4 from file: 457)
DIALOG(R)File 457:The Lancet

0000054101
USE FORMAT 7 OR 9 FOR FULL TEXT
Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: Group randomised trial
O'Brien, Katherine L; Moulton, Lawrence H; Reid, Raymond; Weatherholtz, Robert; Et al
The Lancet vol. 362, 9381 PP: 355-61 Aug 2, 2003 DOCUMENT TYPE: PERIODICAL; Clinical Trial LANGUAGE: English RECORD TYPE: New; Fulltext
WORD COUNT: 6392

Efficacy and safety of seven-valent conjugate pneumococcal vaccine in American Indian children: Group randomised trial
ABSTRACT:
...group-randomised study, we have shown that PnCRM7 vaccine has high total efficacy against invasive pneumococcal disease in an American Indian population with a high burden of such disease. The reported primary efficacy of 76(middot)8% (95% CI -9(middot)4 to 95(middot)1%) against vaccine serotype disease does not differ from that of 97(middot)4% (79(middot)6-98(middot)5) reported in the NCKP study, the only other published study of efficacy against invasive pneumococcal disease of any conjugate pneumococcal vaccine product. Because about half of all invasive pneumococcal disease in children younger than 2 years on the Navajo Nation is caused by serotypes not included in the PnCRM7 vaccine, the efficacy against all serotype pneumococcal disease was 54(middot)1%.6 This rate is in striking contrast to the 89(middot)1% reduction in all cases of invasive pneumococcal disease in the NCKP study.
BACKGROUND: Streptococcus pneumoniae is the main cause of invasive bacterial disease in children aged younger than 2 years. Navajo and White Mountain Apache children have some of the highest rates of invasive pneumococcal disease documented in the world. We aimed to assess the safety and efficacy of a seven-valent polysaccharide protein conjugate pneumococcal vaccine (PnCRM7) against such disease.
METHODS: In a group-randomised study, we gave this vaccine...

...than 2 years from the Navajo and White Mountain Apache Indian reservations; meningococcal type C conjugate vaccine (MnCC) served as the control vaccine. Vaccine schedules were determined by age at enrollment. We recorded episodes of invasive pneumococcal disease and serotyped isolates. Analyses were by intention to treat and per protocol.
FINDINGS: 8292...
...efficacy group (children enrolled by 7 months of age) there were eight

cases of vaccine serotype disease in the controls and two in the PnCRM7 group; in the intention-to-treat analysis we noted 11 cases of vaccine serotype disease in the MnCC control group and two in the PnCRM7 group. After group randomisation...

...controlled for, the per protocol primary efficacy of PnCRM7 was 76.8% (95% CI -9.4% to 95.1%) and the intention-to-treat total primary efficacy was 82.6% (21.4% to 96.1%). INTERPRETATION: PnCRM7 vaccine prevents vaccine serotype invasive pneumococcal disease even in a high risk population. Other regions with similar disease burden should consider...

TEXT:

Summary

Background Streptococcus pneumoniae is the main cause of invasive bacterial disease in children aged younger than 2 years. Navajo and White Mountain Apache children have some of the highest rates of invasive pneumococcal disease documented in the world. We aimed to assess the safety and efficacy of a seven-valent polysaccharide protein conjugate pneumococcal vaccine (PnCRM7) against such disease.

Methods In a group-randomised study, we gave this vaccine...

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Findings 8292...

...efficacy group (children enrolled by 7 months of age) there were eight cases of vaccine serotype disease in the controls and two in the PnCRM7 group; in the intention-to-treat analysis we noted 11 cases of vaccine serotype disease in the MnCC control group and two in the PnCRM7 group. After group randomisation...

...for, the per protocol primary efficacy of PnCRM7 was 76-8% (95% Cl -9(middot)4% to 95(middot)1%) and the intention-to-treat total primary efficacy was 82(middot)6% (21(middot)4% to 96(middot)1%).

Interpretation PnCRM7 vaccine prevents vaccine serotype invasive pneumococcal disease even in a high risk population. Other regions with similar disease burden should consider including this vaccine in the routine childhood vaccine schedule.

Introduction

Streptococcus pneumoniae (pneumococcus) is a major cause of morbidity and mortality in people of all ages, but especially...

...extremes of age, and in those who live in developing countries. Before the introduction of pneumococcal conjugate vaccine, the rate of invasive pneumococcal disease in children younger than 2 years was 166(middot)9 per 100000 child-years in the USA.1 The burden of invasive pneumococcal disease in young children in developing countries is substantially higher than that in developed countries. For example, the incidence of invasive pneumococcal disease in children younger than 12 months was reported to be 224 and 349 per 100 000 in The Gambia and South Africa, respectively.2,3 Rates of non-bacteraemic pneumococcal pneumonia in young children are estimated to be two to ten times those of invasive disease. There are an estimated 1 (middot)9 million deaths worldwide from acute respiratory illness in children younger than 5 years each year, many of these deaths are caused by S pneumoniae.4

People of the Navajo and White Mountain Apache tribes in southwestern USA, and Alaska Native populations are at high risk of invasive pneumococcal disease.5-8 Between 1983 and 1990, the rate of invasive pneumococcal disease in White Mountain Apache children

younger than 2 years was 1820 per 100 000...

...general US population. Reasons for the increased risk of disease are unknown.

For young children, pneumococcal polysaccharide vaccines provide little protection against pneumococcal disease because those younger than 2 years of age respond poorly to T-cell independent...

...capable of mounting a brisk immune response to T-cell dependent antigens. As a result, serotype-specific pneumococcal polysaccharide-protein conjugate vaccines, which result in a T-cell dependent immune response have been developed. One such vaccine, a seven-valent pneumococcal vaccine conjugate to CRM sub 197 (PnCRM7), has proved efficacious against invasive pneumococcal disease in children younger than 2 years of age in a Northern California population sup 9 and against pneumococcal otitis media in young children in Finland.10

We aimed to determine the efficacy of this pneumococcal conjugate vaccine against invasive pneumococcal disease in American Indian children at high risk of invasive pneumococcal disease. Unlike the Northern California Kaiser Permanente (NCKP) study, we used a group-randomised design...

...The White Mountain Apache tribe consists of about 14000 enrolled members, and the reservation, roughly 1(middot)6 million acres in size, is located in central Arizona. The Whiteriver service unit...units were concealed from study staff and participants.

The intervention vaccine was a seven-valent (4, 6B, 9V, 14, 18C, 19F, 23F) pneumococcal polysaccharide protein conjugate vaccine, PnCRM7 (Wyeth Vaccines, Pearl River, NY, USA). Each 0(middot)5 mL dose of PnCRM7 vaccine contained 2 (mu)g each of serotypes 4, 9V, 14, 19F, and 23F polysaccharides; 2 (mu)g of serotype 18C oligosaccharide; 4 (mu)g of serotype 6B polysaccharide, all independently conjugated to the protein carrier CRM sub 197 protein; and 0(middot)5 mg of aluminum phosphate as an adjuvant.

The control vaccine was Neisseria meningitidis group-C protein conjugate vaccine, MnCC (Wyeth Vaccines), which is an unlicensed investigational vaccine in the USA. Every 0(middot)5 mL dose of MnCC vaccine contained 10 (mu)g of group-C oligosaccharides coupled to CRM sub 197 by reductive amination, and 0(middot)5 mg of aluminum phosphate as an adjuvant.

Infants in the primary efficacy group were those...

...6 weeks and 7 months, received three doses of vaccine 2 months apart (minimum of 4 weeks apart), and a booster dose at 12-15 months of age (at least 2...

...7-11 catch-up group) received two doses of vaccine 2 months apart (minimum of 4 weeks) and a booster dose at age 12-15 months (at least 2 months after...

...Children enrolled in the study received routine childhood vaccines along with the study vaccine (table 1).

All enrolled children were followed up for serious adverse events, which were defined as: admission...

...2 years (irrespective of enrolment in the efficacy trial) in whom sepsis, meningitis, or a pneumococcal invasive disease episode was suspected, or who were without focal findings on examination, and had a temperature higher than 39(middot)4(degrees)C, in line with published guidelines.12,13 Furthermore, if a focal infection such...

...fluid, joint fluid, and pleural fluid.
We used laboratory-based active surveillance to detect invasive pneumococcal and meningococcal disease in the study population. We contacted reservations' health facilities to ascertain cases of invasive pneumococcal disease. We reviewed all admissions at IHS hospitals, contract facilities, and referral hospitals for study participants. Subisolates of all positive pneumococcal and meningococcal cultures from normally sterile body fluids were obtained; pneumococcal isolates were serotyped with the Quellung reaction. A random subsample of pneumococcal serotyped isolates and all isolates that were non-typeable were confirmed at the Streptococcal Reference...

...meningococcal isolates.
Statistical analysis
We planned to continue the study until 48 cases of invasive pneumococcal disease had been reported. In ...20% efficacy, if the true vaccine efficacy were 70%. We used a design effect of 1 (middot)2, based on historical Navajo data, to yield a final sample size of 48...

...what has been termed the total effect of the vaccine, which has been previously defined.14 This effect is a combination of the direct effect (that conferred to individuals because they...

...large number of other individuals have received the vaccine, thus reducing exposure to the organism).14 The direct effect is what is usually estimated in individually-randomised trials.
All enrolled children...

...on or before May 31, 2000 (including episodes of disease after age 24 months). Invasive pneumococcal disease episodes were categorised as vaccine type (ie, 4, 6B, 9V, 14, 18C, 19F, or 23F), and non-vaccine type if the serotype was anything other than these, including non-typeable isolates. Numerator outcomes for the primary efficacy...

...qualified for the per protocol analysis if they occurred during a window of time starting 14 days after the primary series and ending at 16 months of age if the booster...
...11 catch-up group qualified for the per protocol analysis if they occurred at least 14 days after completion of three doses of study vaccine and for the 12-23 catch-up group if they arose at least 14 days after the second dose. Outcomes that occurred at any time after the first dose...

...regression models with an over-dispersion parameter. This parameter accounts for within-randomisation unit correlation.14 The time from first immunisation (intention-to-treat analysis) or per protcol-qualifying immunisation (per...

...date of culture or censoring was used as the exposure time. Efficacy was calculated as (1-risk ratio (RR))x100, where RR is the rate of infection in children who had...

...two study vaccine groups were compared with Fisher's exact test for several time periods (3 days, 7 days, 30 days, and the entire follow-up period after a dose), vaccine...

...who were ineligible and those whose parents declined to participate, we enrolled 8292 (76(middot)3%) infants in the study between April 30, 1997, and Dec 31, 1999. Therefore, about 60...
...age-eligible population participated in the trial. Of the 8292 enrolled infants, 8091 (97(middot)5%) resided in one of the 38 units of

randomisation. The remaining 201 infants resided in...

...included in analyses because their vaccine was not randomly allocated. None of these children had pneumococcal invasive disease.

Table 3 shows vaccine allocation by study group. 46 (0(middot)6%) children received at least one...cases showed a significant public health benefit for the study population.

Primary efficacy group

Table 4 shows characteristics of participants in the primary efficacy group. Efficacy estimates, case splits, and denominators for various per protocol and intention-to-treat analyses are in table 5. Between April 30, 1997,and May 31, 2000, ten cases of per protocol vaccine serotype invasive pneumococcal disease arose in children in the primary efficacy group-eight in the MnCC control group and two (serotypes 9V and 14) in participants who received PnCRM7. Of these ten cases, six were in separate randomisation units...

...per protocol total primary efficacy of PnCRM7 was 76(middot)8% (95% CI -9(middot)4% to 95(middot)1%) and the intention-to-treat total primary efficacy was 82(middot)6% (21(middot)4% to 96(middot)1 %). The serotype distribution of the invasive primary efficacy cases is shown in table 6.

Two children developed invasive pneumococcal disease after PnCRM7 vaccination. The first child received three doses of PnCRM7 vaccine at age ...

...cell count of 33 200, a right middle-lobe infiltrate on chest radiograph, and type 9V pneumococcus isolated from blood culture. The second child received three doses of PnCRM7 at age 2, 4, and 8 months. At 9(middot)6 months of age, 53 days after the third...

...child had a white blood-cell count of 7700 and a normal chest radiograph. Type 14 pneumococcus was isolated from blood culture. This second child was also enrolled in a nested immunogenicity...

...report of vaccine immunogenicity in this population. Neither of the two children with breakthrough vaccine serotype invasive disease had any evidence of immunodeficiency in their history, from their physical examination, or...

...follow-up to age 2 years.

Catch-up groups

One vaccine-type case of invasive pneumococcal disease (type 14 bacteraemia) was noted in the 610 children from randomised communities enrolled in the 7-11...

...was in a child who had been given MnCC vaccine. Likewise, one vaccine-type invasive pneumococcal disease episode occurred in the 1689 children from randomised communities enrolled at age 12-23 months. This was a type 14 bacteraemia, which was also in a child who had received MnCC.

Clinical syndromes

Of the 16 vaccine-type cases in participants from randomised communities, 15 had S pneumoniae isolated from a blood culture and one child had S pneumoniae isolated from the cerebrospinal fluid. The clinical syndromes documented at the time of discharge for these invasive pneumococcal disease episodes were: otitis media (six), bacteraemia without a source (five); pneumonia (four); and meningitis (one).

Non-vaccine-type invasive disease

There were 18 episodes of invasive, non-vaccine serotype disease (11 from the PnCRM7 group and seven in children who had MnCC); 13 of...

...intention-to-treat case splits reached statistical significance. The

serotypes represented were: 12F (eight cases), 7F (two cases), 5 (two cases) and one each of 3, 6A, 18B, 19A, 23B, and 38. Of the 18 episodes of non-vaccine type invasive disease that occurred, clinical diagnoses at discharge were: otitis media (two); bacteraemia without a source (11); pneumonia (three); and meningitis (two).

Safety

During the study, 981 (22(middot)8%) PnCRM7 and 886...

...diagnoses in this category), in the primary efficacy group with 19 who received PnCRM7 and 5 who had MnCC; and otitis media in the 12-23 catch-up group, with 12...

...died, 15 who had received PnCRM7 and seven who had had MnCC (p=0(middot)14). Of the deaths, 11 resulted from injuries (eg, drowning, house fires, motor vehicle accidents, suffocation...

...group and three in PnCRM7), and one each of viral myocarditis (MnCC), Respiratory Syncytial Virus pneumonia (MnCC), type 5 pneumococcal sepsis (PnCRM7), histiocytosis (PnCRM7), brain cancer (PnCRM7), and apnoea or seizure of unknown cause (PnCRM7...group-randomised study, we have shown that PnCRM7 vaccine has high total efficacy against invasive pneumococcal disease in an American Indian population with a high burden of such disease. The reported primary efficacy of 76(middot)8% (95% CI -9(middot)4 to 95(middot)1%) against vaccine serotype disease does not differ from that of 97(middot)4% (79(middot)6-98(middot)5) reported in the NCKP study, the only other published study of efficacy against invasive pneumococcal disease of any conjugate pneumococcal vaccine product. Because about half of all invasive pneumococcal disease in children younger than 2 years on the Navajo Nation is caused by serotypes not included in the PnCRM7 vaccine, the efficacy against all serotype pneumococcal disease was 54(middot)1%.6 This rate is in striking contrast to the 89(middot)1% reduction in all cases of invasive pneumococcal disease in the NCKP study.

Rates of invasive pneumococcal disease and the proportion that are included in the seven-valent conjugate pneumococcal vaccine used in children on the Navajo Nation are very similar to those in many developing countries around the world. The performance of conjugate pneumococcal vaccines is likely to vary in accordance with many epidemiological and population characteristics, including age at acquisition of 5 pneumoniae in the nasopharynx, density and frequency of pneumococcal nasopharyngeal colonisation, rate of invasive pneumococcal disease, rate of non-invasive pneumococcal disease, pneumococcal serotype distribution, crowding, exposure to other children, exposure to paniculate matter from smoke, coincident respiratory viral...

...for expected vaccine efficacy in some developing world settings with high burden of disease, broad serotype distribution, and where HIV infection is not prevalent.

If increases in non-vaccine serotype invasive disease are going to occur as a result of community antibody pressure from administration of conjugate pneumococcal vaccine products, they are most likely to occur in settings where circulation of non-vaccine...

...group than were in the MnCC control group (12 and 8, respectively). Thus, surveillance for serotype-specific invasive disease in this population will be essential to provide continuing information about the effect of community-wide use of conjugate pneumococcal vaccine.

In the Finnish Otitis Media trial of PnCRM7 and another investigational conjugate pneumococcal vaccine (PnOMPC (Merck, Bluebell, PA, USA)), replacement otitis media with non-vaccine serotypes was noted...

...product.10,15 Up to now, there has been no such significant events for invasive pneumococcal disease in the NCKP population or in this American Indian population.
Our study design allowed...

...effects when a large proportion of young children in a community are immunised with a conjugate pneumococcal vaccine product.
Although the number of children included in the analysis was only 1299, there were no cases of vaccine serotype invasive disease in children who were vaccinated with PnCRM7 at age V months or older. Furthermore, there were no cases of vaccine serotype pneumococcal disease in partly immunised PnCRM7 randomised children at any age.
We did note two cases of disease after three doses of PnCRM7 vaccine. One of these children had a classic pneumococcal-associated lobar pneumonia. The other child had an occult bacteraemia syndrome that resolved without antibiotics. Neither of these...effective sample size, and mixing of the intervention and control populations. The rate of invasive pneumococcal disease in the control study participants (ie, those aged <24 months) during the course of...

...a reduced propensity to obtain blood cultures from febrile children in an era of routine conjugate Haemophilus influenzae type b vaccine use. Furthermore, there has been a shift away from vaccine serotypes: in our study, only 11 of 18 (61%) invasive pneumococcal cases in the MnCC control group were vaccine serotypes. The combination of these lower rates...

...fairly low precision of our efficacy estimates.
The PnCRM7 vaccine was highly efficacious against vaccine serotype invasive pneumococcal disease in this high-risk population. We have shown the robust nature of the PnCRM7...

...disease not only in a general US population setting but also in a setting where pneumococcal colonisation frequency is 50% at 2 months of age, and the invasive disease incidence has been among the highest documented worldwide.
Conjugate pneumococcal vaccine provides significant public health benefit in this high risk population and should be considered as part of the routine childhood vaccination schedule in other countries or regions with high pneumococcal disease burden.
Acknowledgments
We thank the Navajo and White Mountain Apache tribes, the Indian Health ...
CAPTIONS:
Table 1: Schedule of routine vaccinations for participants
Table 2: Criteria for inclusion in subgroup analyses
Trial profile
Table 3: Vaccine allocation by study group and main reasons for exclusion from per protocol analysis
Table 4: Characteristics of participants in the primary efficacy group
Table 5: Frequency of invasive disease and PnCRM7 vaccine efficacy by analysis group and vaccine type
Table 6: Serotype distribution of invasive disease in primary efficacy group as of May 31, 2001
CITED REFERENCES:
References
1 Robinson K, Baughman W, Rothrock G, et al. Epidemiology of invasive Streptococcus pneumoniae infections in the United States, 1995-1998: opportunities for prevention in the conjugate vaccine era. JAMA 2001; 285: 1729-35.
2 Usen S, Adegbola R, Mulholland K, et al. Epidemiology of invasive

pneumococcal disease in the Western Region, The Gambia. Pediatr Infect Dis J 1998; 17: 23-28.
3 Karstaedt A, Khoosal M, Crewe-Brown H. Pneumococcal bacteremia during a decade in children in Soweto, South Africa. Pediatr Infect Dis J 2000; 19: 454-57.
4 Williams BG, Gouws E, Boschi-Pinto C, Bryce J, Dye C. Estimates of world-wide distribution of child deaths from acute respiratory infections. Lancet 2002; 2: 25-32.
5 Cortese MM, Wolff M, Almeido-Hill J, Reid R, Ketcham J, Santosham M. High incidence rates of invasive pneumococcal disease in the White Mountain Apache population. Arch Intern Med 1992; 152: 2277-82.
6...

...Croll J, Parkinson AJ, Reid R, Santosham M. Active laboratory-based surveillance for invasive Streptococcus pneumoniae (pneumococcus) among Navajo people in the American Southwest, 1989-1996. American Society of Microbiology 39th Interscience...

...26-29, 1999. Abstract 1187.
7 Davidson M, Schraer CD, Parkinson AJ, et al. Invasive pneumococcal disease in an Alaska Native population, 1980 through 1986. JAMA 1989; 261: 715-18.
8...

...M, Parkinson AJ, Bulkow LR, Fitzgerald MA, Peters HV, Parks DJ. The epidemiology of invasive pneumococcal disease in Alaska, 1986-1990: ethnic differences and opportunities for prevention. J Infect Dis 1994...

...9 Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000; 19: 187-95.
10 Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 2001; 344: 403-09.
11 Moulton LH, O'Brien KL, Kohberger R, et al. Design of a group-randomized Streptococcus pneumoniae vaccine trial. Controlled Clin Trials 2001; 22: 438-52.
12 Baraff LJ, Bass JW, Fleisher...

...and children O to 36 months of age with fever without source. Pediatrics 1993; 92: 1-12.
13 American College of Emergency Physicians. Clinical policy for the initial approach to children...

...the age of 2 years presenting with fever. Ann Emerg Med 1993; 22: 628-37.
14 Halloran ME, Haber M, Longini IM, Struchiner CJ. Direct and indirect effects in vaccine efficacy...

...Kilpi T, Palmu A, Leinonen M, Eskola J, FinOM Study. Efficacy of a seven-valent pneumococcal conjugate vaccine (PncOMPC) against serotype-specific acute otitis media (AOM) caused by Streptococcus pneumoniae (Pnc). American Society of Microbiology 40th Interscience Conference on Antimicrobial Agents and Chemotherapy. Toronto, Canada...

...245.
16 Rennels MB, Edwards KM, Keyserling H, et al. Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM197 in United States infants. Pediatrics 1998; 101: 604-11.

14/3,K/27 (Item 5 from file: 457)
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Effect of conjugate pneumococcal vaccine followed by polysaccharide pneumococcal vaccine on recurrent acute otitis media: A randomised study

Veenhoven, Reinier; Bogaert, Debby; Uiterwaal, Cuno; Brouwer, Carole; Et al

The Lancet vol. 361, 9376 PP: 2189-95 Jun 28, 2003 DOCUMENT TYPE: PERIODICAL; Clinical Trial LANGUAGE: English RECORD TYPE: New; Fulltext
WORD COUNT: 6072

Effect of conjugate pneumococcal vaccine followed by polysaccharide pneumococcal vaccine on recurrent acute otitis media: A randomised study

ABSTRACT:

In our study, pneumococcal carriage was noted in 50% of children at study entry. This proportion remained constant throughout follow-up, both in the pneumococcal vaccine group and in controls. Although pneumococcal vaccinations did reduce nasopharyngeal carriage of the seven conjugate vaccine serotypes, including serotype 6B, this reduction was accompanied by an increase in pneumococcal serotypes not included in the conjugate vaccine. This shift in nasopharyngeal pneumococcal carriage after conjugate vaccination is consistent with observations in other studies22,23 and is most probably the result...

...was still unaffected by vaccination (data not shown). By induction of nasopharyngeal replacement with non-conjugate pneumococcal serotypes, PCV could even induce recurrence of AOM, because newly acquired carriage is associated with...

...carriage.28 This risk might account for the increased number of AOM episodes in the pneumococcal vaccine group in our study. The potentially pathogenic capacity of non-conjugate-vaccine pneumococcal serotypes was previously shown in the Finnish infant study on AOM;3 the conjugate vaccine reduced AOM caused by conjugate-vaccine-type pneumococci by 57%, but AOM caused by non-conjugate-vaccine pneumococcal serotypes was increased by 34%.

BACKGROUND: Pneumococcal conjugate vaccine prevents recurrent acute otitis media (AOM) in infants immunised at 2, 4, 6, and 12-15 months of age. We aimed to find out whether this vaccine...
...episodes of AOM. METHODS: In this double-blind, randomised study, we enrolled 383 patients aged 1-7 years who had had two or more episodes of AOM in the year before...

...episodes (two or three episodes vs four or more episodes). Children received either 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal polysaccharide vaccine, or hepatitis A or B vaccines. They were followed up for 18 months...

...We also cultured samples of middle-ear fluid and nasopharyngeal swabs to assess association of pneumococcal serotypes with AOM after vaccination. FINDINGS: We noted no reduction of AOM episodes in the pneumococcal vaccine group compared with controls (intention-to-treat analysis: rate ratio 1.25, 95% CI 0.99-1.57). Although nasopharyngeal carriage of pneumococci of serotypes included in the conjugate-vaccine was greatly reduced after pneumococcal vaccinations, immediate and complete replacement by non-vaccine pneumococcal serotypes took place. INTERPRETATION: These data do not lend support to the use of pneumococcal conjugate vaccine to

prevent otitis media in previously unvaccinated toddlers and children with a history of...
TEXT:
Summary
Background Pneumococcal conjugate vaccine prevents recurrent acute otitis media (AOM) in infants immunised at 2, 4, 6, and 12-15 months of age. We aimed to find out whether this vaccine...

...episodes of AOM.
Methods In this double-blind, randomised study, we enrolled 383 patients aged 1-7 years who had had two or more episodes of AOM in the year before...

...episodes (two or three episodes vs four or more episodes). Children received either 7-valent pneumococcal conjugate vaccine followed by 23-valent pneumococcal polysaccharide vaccine, or hepatitis A or B vaccines. They were followed up for 18 months...

...We also cultured samples of middle-ear fluid and nasopharyngeal swabs to assess association of pneumococcal serotypes with AOM after vaccination.
Findings We noted no reduction of AOM episodes in the pneumococcal vaccine group compared with controls (intention-to-treat analysis: rate ratio 1(middot)25, 95% Cl 0(middot)99-1 (middot)57). Although nasopharyngeal carnage of pneumococci of serotypes included in the conjugate-vaccine was greatly reduced after pneumococcal vaccinations, immediate and complete replacement by non-vaccine pneumococcal serotypes took place.
Interpretation These data do not lend support to the use of pneumococcal conjugate vaccine to prevent otitis media in previously unvaccinated toddlers and children with a history of...

...361: 2189-95
Introduction
The American Academy of Pediatrics has recommended immunisation with 7-valent pneumococcal conjugate vaccine (PCV7) for children with recurrent or severe acute otitis media (AOM) and children who have tympanostomy tubes because of recurrent AOM.1 This advice was based on the results of two clinical trials with PCV7. The trials included almost 40 000 healthy infants, who were immunised at 2, 4, and 6 months of age, and had booster vaccinations at 12-15 months of age.2,3 These children were followed up for the occurrence of AOM up to their second birthday. The pneumococcal vaccine reduced the number of infants with recurrent episodes of AOM by 9%. The largest...

...number of children receiving tympanostomy tubes was reduced by 20%.2
However, the benefits of pneumococcal conjugate vaccine have not been investigated in previously unvaccinated toddlers and older children who have documented...

...since children with recurrent AOM can have subtle immunodeficiencies that alter the vaccine's immunogenicity.4-6 Genetically determined factors in innate and adaptive immunity may also affect the effectiveness of...

...vaccine effectiveness in older children might differ from that in infants due to differences in pneumococcal serotype coverage and environmental factors.9 Therefore, the efficacy of pneumococcal conjugate vaccine needs to be assessed in randomised trials to support recommendations that these children should also be immunised.
We investigated whether combined vaccination with PCV7 followed by 23-valent pneumococcal polysaccharide vaccine (PPSV23) could prevent AOM in children aged 1-7 years, with two or more documented episodes

of AOM before vaccination. This combination was chosen because of the booster effect of the polysaccharide vaccine after priming with conjugate vaccine both in infants and in children prone to otitis.10,11 Furthermore, the broad pneumococcal serotype coverage by the 23-valent vaccine could benefit children older than 2 years of age. We assessed the protective efficacy of pneumococcal vaccination against recurrent AOM, and the effect of vaccination on culture-confirmed pneumococcal AOM and nasopharyngeal carriage.

Methods

We did a randomised, double-blind trial between April, 1998...

...were two or more episodes of AOM in the year before study entry, and age 1-7 years. The number of previous AOM episodes was based both on parental report-with...

...Prevnar, Wyeth, Rochester, NY, USA) consisted of 2 (mu)g each of capsular polysaccharides of pneumococcal serotypes 4, 9V, 14, 19F, and 23F, 4 (mu)g of serotype 6B polysaccharide, and 2 (mu)g of serotype 18C oligosaccharide, each conjugated individually to the CRM197 protein. PPSV23 (Pneumune, Wyeth) consisted of 25 (mu)g of capsular polysaccharides of each of the pneumococcal serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B3 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F. Control vaccines were recombinant hepatitis B vaccine (Engerix-B=AE Junior, GlaxoSmithkline, Rixenart...that parents and physicians were unaware of treatment. Children aged 12-24 months in the pneumococcal vaccine group were immunised with PCV7 twice (with a 1-month interval between immunisations) followed 6 months later by PPSV23. The control vaccine group aged...

...B vaccinations according to a similar time schedule. Children aged 25-84 months in the pneumococcal vaccine group received one dose of PCV7, followed 7 months later by PPSV23. The control...

...25-84 months received hepatitis A vaccine twice.

The primary endpoint was the efficacy of pneumococcal vaccination against clinical episodes of AOM during a follow-up period of 18 months, starting 1 month after completion of the vaccination scheme. AOM episodes occurring during the 6-7 month period beginning 1 month after PCV7 or control vaccinations and ending 1 month after the last vaccination were also recorded. We instructed parents to visit the study...

...of acute infection: acute earache, new-onset otorrhoea, irritability, or fever greater than 38(middot)5(degrees)C rectally or 38(middot)0(degrees)C axillary.12 New episodes of AOM...

...treatment.

Additional outcomes in our study included number of AOM episodes due to the seven pneumococcal serotypes included in the conjugate vaccine and nasopharyngeal carriage of conjugate vaccine serotypes. Bacterial cultures from middle-ear fluid were obtained only once in every child, at the time of the first AOM episode arising at least 1 month after the last vaccination. Parents had been asked to bring their child to the...

...Samples of middle-ear fluid and nasopharyngeal swabs were plated within 6 h onto two 5% sheep blood agar plates, a 5% sheep blood agar plate with 5 mg/L gentamicin, and a chocolate agar plate. Agar plates were incubated at 37(degrees...

...agar plate with gentamicin and the chocolate agar plate with raised CO2. Identification of Streptococcus pneumoniae, Haemophilus influenzae

and Moraxella catarrhalis was based on colony morphology and conventional methods of determination. When S pneumoniae was isolated, we undertook serotyping with the capsular swelling method (Quellung reaction) by microscopy with...

...a diary for as long as symptoms persisted. At follow-up visits scheduled at 7, 14, 20, and 26 months after randomisation, AOM registration forms filled in by the physicians and...
...and throat operations. Between these scheduled visits, study physicians contacted the parents by telephone every 3 months. Previous to and 1 month after each vaccination, a blood sample was taken for immunological assessment.

Concentrations of IgG to the seven pneumococcal serotypes in the conjugate vaccine were measured in serum by ELISA.13 All laboratory work was done by individuals...

...25% to a recurrence rate of 40% of one or more AOM episodes in the pneumococcal vaccine group to be clinically relevant. In order to detect such a reduction, with a...

...analysis in S-plus, version 2000; all other analyses were done with SPSS 10(middot)1. Results are presented as rate ratios with 95% CI; we judged significance to be reached when CI did not include 1. We did both intention-to-treat and per-protocol analyses.

The differences in conjugate and non-conjugate nasopharyngeal pneumococcal carriage between the treatment groups were assessed as follows: children were classified as having had a positive culture for any pneumococcal serotype included in PCV7 or any pneumococcal serotype not included in PCV7 if they had such a positive culture at any of the scheduled follow-up visits after complete vaccination. Proportional differences in pneumococcal carriage and pathogens causing AOM were analysed with (chi) sup 2 tests or Fisher's...

...enrolled 383 children between April, 1998, and January, 2001; 190 children were randomised to receive pneumococcal vaccinations and 193 to receive control hepatitis vaccinations (figure 1). Age, sex, number of previous AOM episodes, and other risk factors for AOM did not differ between the groups (table 1). In the pneumococcal vaccine group, 186 of 190 children (98%) completed the vaccination scheme, as did 181 of 193 controls (94%). The median follow-up after complete vaccination was similar in the pneumococcal vaccine group (18(middot) 1 months, range 2(middot)4-23(middot)0) and control group (18(middot)0 months, range 0(middot)5-23(middot)0). One patient was lost to follow-up immediately after the first vaccination. No serious adverse events were noted after pneumococcal or hepatitis vaccinations.

Of the 475 AOM episodes diagnosed during follow-up after the final vaccination, 275 episodes were recorded in 107 of 186 children (58%) in the pneumococcal vaccine group who completed all vaccinations (recurrence rate 1(middot)1 episodes per person-year) and 200 episodes in 101 of 181 controls (56%; recurrence rate...
...per-protocol analysis after complete vaccination, the rate ratio of recurrence of AOM for the pneumococcal vaccine group versus controls was 1(middot)29 (95% CI 1(middot)02-1(middot)62). The results of the intention-to-treat analysis did not differ from those of the per-protocol analysis over the same period (rate ratio 1(middot)25, 95% CI 0(middot)99-1(middot)57). The cumulative hazard function for AOM of the fully vaccinated pneumococcal vaccine group and controls is shown in figure 2. Subgroup analysis suggested a slightly higher rate ratio of recurrence of AOM in the pneumococcal vaccine group than in controls in children older than 2 years at the time of first vaccination (rate ratio 1(middot)45, 95% CI 1(middot)09-1(middot)94),

compared with the group aged 1-2 years (1(middot)07, 0(middot)72-1(middot)60). The rate ratio also seemed higher in children who had two or three episodes of AOM in the year preceding the study (1(middot)66, 1(middot)11-2(middot)49) compared with those who had four or more episodes (1(middot)20, 0(middot)92-1(middot)56). However, since neither of the interactions between age and treatment effect (1(middot)37, 0(middot)87-2(middot)14) and between previous AOM episodes and treatment effect (0(middot)74, 0(middot)45-1(middot)22) was significant, we were not able to conclude that rate ratios differed across...

...year before study entry from the analyses did not change the outcome of the study (1(middot)30, 0(middot)83-2(middot)06).

We recorded a total of 840 episodes...

...those that arose in the period of 6-7 months between first study vaccinations and 1 month after the last vaccination. 445 episodes were in 135 of the 190 children (71%) in the pneumococcal vaccine group (recurrence rate 1(middot)23 episodes per person-year), and 395 episodes in 139 of the 192 controls (72%; recurrence rate 1(middot)08 episodes per person-year). During this whole period, the intention-to-treat analysis also showed no decrease of AOM in the pneumococcal vaccine group compared with controls (rate ratio 1(middot)11, 95% CI 0(middot)92-1(middot)33).

We used data from the diaries to assess the severity and duration of...

...follow-up completed diaries for 399 of the 475 episodes. We noted no differences between pneumococcal vaccine group and controls in median days per episode for ear-related symptoms such as...

...The number of children treated with tympanostomy tubes during follow-up was similar in the pneumococcal vaccine and control groups (33 and 39, respectively; p = 0(middot)36).

Nasopharyngeal swabs were...

...375, 358, 346, 282, and 240 of the children, respectively. At baseline, nasopharyngeal carriage of S pneumoniae was found in 49% of all children, regardless of age. Of these nasopharyngeal pneumococcal serotypes, 53% had been included in PCV7; these were serotypes 19F (13%), 6B (12%), 23F (11%), 14 (9%), 9V (5%), 18C (1%), and 4 (1%). In the pneumococcal vaccine group the nasopharyngeal carriage of the conjugate vaccine serotypes fell substantially after complete vaccination compared with the control group (p<0(middot)001). However, overall nasopharyngeal carriage of pneumococci was not affected by pneumococcal vaccination, because of a concurrent significant increase in non-conjugate-vaccine serotypes (p=0(middot)04; figure 3). Booster vaccination with PPSV23 did not seem to prevent carriage of serotypes not included in the conjugate vaccine. The largest reduction in carriage of conjugate vaccine serotypes (69%) was noted for serotype 18C (p=0(middot)03); the lowest reduction (30%) was found for serotype 6B (p=0(middot)29). Replacement by non-conjugate vaccine serotypes was mainly caused by serotypes 11 (p=0(middot)01) and 15 (p=0(middot)02), even though these serotypes were included in PPSV23, and by serotype 16 (p= 0(middot)03), which was not included in PPVS23. Carriage rate of cross-reacting pneumococcal serotype 6A did not differ between the pneumococcal vaccine and control groups (p=0(middot)47).

We took no more than one sample...

...Middle-ear fluid was obtained from 92 of 107 children (86%) with AOM in the pneumococcal vaccine group and 89 of 101 controls (88%; table 2). S pneumoniae was isolated more often in middle-ear fluid samples in controls (21%) than in the pneumococcal vaccine group (14%).

4% of middle-ear fluid samples from the pneumococcal vaccine group were positive for pneumococcal serotypes included in PCV7, compared with 9% of controls. These numbers were too small for...

...group A streptococci, and P aeruginosa did not differ between the groups. However, we isolated 5 aureus more often in the pneumococcal vaccine group than in the control group (26 vs nine children, p=0(middot)002). All 5 aureus cultures and P aeruginosa cultures were derived from spontaneous drainage of ears; 75% of the children had ventilation tubes.

IgG anti-pneumococcal antibody concentrations were measured for 126 randomly selected children, 24 from each of the four randomisation groups who received pneumococcal vaccines and 30 controls. Geometric mean concentrations of these antibodies were consistently higher in the pneumococcal vaccine group than in controls, and reached values far above 1(middot)5 mg/L, apart from concentrations of serotype 6B, which remained below 0(middot)2 mg/L (table 3).

Discussion

Our results show that combined pneumococcal conjugate and polysaccharide vaccination is not effective in prevention of AOM in children older than 1 year of age with recurrent AOM. Exclusion of children who were severely prone to otitis...

...investigation.

During the trial we saw a marked reduction in AOM episodes both in the pneumococcal vaccine and control groups to an average of one episode per child per year. This...

...study entry; such overestimation has been reported previously in studies of children with recurrent AOM.14 Furthermore, spontaneous recovery of recurrent AOM with increasing age would have had a role in...

...rate of AOM episodes per person-year decreased in the total group of patients from 1(middot)63 in the interval between first and last vaccination to 0(middot)97 between...

...up. On the basis of results from previous trials with PCV7 in healthy infants,2,3 we assumed the efficacy of the vaccine to be higher in children with increased baseline...

...would be unlikely to change these estimates.

We noted very good IgG antibody responses to pneumococcal vaccination in our group of children with recurrent otitis. These responses were significantly higher than those reported in the California and Finnish infant studies,2,3 except for those to serotype 6B.
Recent data from the Finnish otitis media study group also show higher concentrations of antibody in infants after booster vaccination with the polysaccharide vaccine at 14 months of age, compared with PCV7 booster vaccination, which was associated with a better clinical protection against AOM caused by serotype 19F.18 The deficient response to serotype 6B in our study might be due to a subtle immune deficiency, which is characteristic of...

...when healthy infants and toddlers were vaccinated with PCV, they were less likely to carry serotype 6B and cross-reactive serotype 6A or have AOM caused by these pathogens.3,20 By contrast, we found a low effect of pneumococcal vaccination against carriage of serotype 6B and no effect against 6A. This finding is probably the result of the low titres of antibody against serotype 6B, and might have influenced the outcome of our study, since serotypes 6B and 6A are among the most common AOM serotypes.3

Our findings of no beneficial effect of pneumococcal vaccinations contrast with those of the two landmark studies on prevention of AOM by PCV7 in infants.2,3 These investigations both showed a small but beneficial effect on AOM and improved results in...

...age the child has not yet developed AOM and does not have fully established nasopharyngeal pneumococcal carriage.21 S pneumoniae is a frequent pathogen in early AOM.9 Because of inflammation and subsequent damage to the middle-ear mucosa and eustachian tube, early pneumococcal AOM could predispose infants to recurrent AOM caused by other pathogens such as H influenzae, which was shown to become increasingly important in recurrent AOM episodes.9 Arguably, conjugate vaccination at infant age might prohibit or delay nasopharyngeal acquisition of the most frequent pneumococcal serotypes, preventing or delaying pneumococcal AOM until a later age, at which time the child is immunologically and anatomically more...
...and more capable of handling an AOM infection than in infancy. Thus, prevention of early pneumococcal AOM could be especially important for the prevention of the otitis-prone condition.

In our study, pneumococcal carriage was noted in 50% of children at study entry. This proportion remained constant throughout follow-up, both in the pneumococcal vaccine group and in controls. Although pneumococcal vaccinations did reduce nasopharyngeal carriage of the seven conjugate vaccine serotypes, including serotype 6B, this reduction was accompanied by an increase in pneumococcal serotypes not included in the conjugate vaccine. This shift in nasopharyngeal pneumococcal carriage after conjugate vaccination is consistent with observations in other studies22,23 and is most probably the result...

...was still unaffected by vaccination (data not shown). By induction of nasopharyngeal replacement with non-conjugate pneumococcal serotypes, PCV could even induce recurrence of AOM, because newly acquired carriage is associated with...

...carriage.28 This risk might account for the increased number of AOM episodes in the pneumococcal vaccine group in our study. The potentially pathogenic capacity of non-conjugate-vaccine pneumococcal serotypes was previously shown in the Finnish infant study on AOM;3 the conjugate vaccine reduced AOM caused by conjugate-vaccine-type pneumococci by 57%, but AOM caused by non-conjugate-vaccine pneumococcal serotypes was increased by 34%.

We were not able to confirm that replacement took place...

...ear fluid cultures investigated was small. We noted a 51% reduction in AOM caused by conjugate-vaccine-serotype pneumococci, and overall pneumococcal AOM was reduced by 34%; this finding was similar to that of the Finnish study.3 We noted no difference between the groups in presence of other middle ear pathogens, apart from 5 aureus. This species was noted more often in middle-ear fluid cultures from the pneumococcal vaccine group, although only in samples taken from spontaneously draining ears. Whether 5 aureus is a true AOM pathogen or is the result of contamination from the external...

...canal is uncertain,29,30 but the double-blind nature of our study suggests that pneumococcal vaccination has an effect on the isolation of S aureus in samples from spontaneously draining ears.

To summarise, we found that pneumococcal conjugate vaccination combined with pneumococcal polysaccharide vaccination does not prevent AOM in children older than 1 year who have had recurrent episodes of AOM before vaccination. Therefore, pneumococcal vaccinations are not indicated in the management of recurrent AOM in

toddlers and older children. In view of the results of other studies, we might conclude that to prevent pneumococcal AOM in general, and to protect children from developing the otitis-prone condition, pneumococcal vaccinations should be given early in life, at least before 12 months of age and...

...the study, did recruitment, obtained data, did follow-up, and analysed data. D Bogaert undertook pneumococcal serotyping. C Uiterwaal helped to design the study and did statistical analyses. C Brouwer and...

...at the Regional Laboratory of Public Health, Haarlem. P Hermans and R de Groot supervised pneumococcal serotyping. B Zegers and W Kuis helped to plan the trial. G Rijkers helped to...
CAPTIONS:
Figure 1: Trial profile
*One child discontinued treatment because of gastroenteritis directly after first vaccination (link with...

...common variable immune deficiency was diagnosed immedately after first vaccination; one for unknown reasons.
Table 1: Baseline characteristics, ear, nose, and throat history, and risk factors for AOM
Figure 2: Cumulative hazard function for risk of AOM
Figure 3: Nasopharyngeal carriage of pneumococci
* Differences in nasopharyngeal carriage of conjugate vaccine and non-conjugate-vaccine pneumococcal serotypes were significant between the two treatment groups (p<0(middot)05, see results section...

...2: Pathogens cultured at the first AOM episode after completion of the vaccination scheme
Table 3: Geometric mean concentrations (mg/L) of IgG anti-pneumococcal antibodies against conjugate vaccine pneumococcal serotypes
CITED REFERENCES:
References
1 Policy statement: recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis (RE9960). Pediatrics 2000; 106: 362-66.
2 Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000; 19: 187-95.
3 Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 2001; 344: 403-09.
4 Herrod HG, Gross S, Insel R. Selective antibody deficiency to Haemophilus influenzae type B capsular...

...vaccination in children with recurrent respiratory tract infection. J Clin Immunol 1989; 9: 429-34.
5 Prellner K, Harsten G, Lofgren B, Christenson B, Heldrup J. Responses to rubella, tetanus, and...

...GT, Tenbergen-Meekes AM, Voorhorst-Ogink MM, Zegers BJM. Immunoglobulin isotype specific antibody responses to pneumococcal polysaccharide vaccine in patients with recurrent respiratory tract infections. Pediatric Research 1995; 37: 812-19...
...cohort of Finnish children followed for the first two years of life. Pediatr Infect Dis 5 2001; 20: 654-62.
10 O'Brien KL, Steinhoff MC, Edwards K, Keyserling H, Thomas ML, Madore D. Immunologic priming of young children by pneumococcal glycoprotein conjugate, but not polysaccharide vaccines. Pediatr Infect Dis J 1996; 15: 425-30.

11 Breukels MA, Rijkers GT, Voorhorst-Ogink MM, Zegers BJM, Sanders EAM. Pneumococcal conjugate vaccine primes for polysaccharide-inducible IgG2 antibody response in children with recurrent otitis media acuta...

...1990; 33: 242-45.
13 Musher DM, Luchi MJ, Watson DA, Hamilton R, Baughn RE. Pneumococcal polysaccharide vaccine in young adults and older bronchitics: determination of IgG responses by ELISA and...

...serum with non-type-specific cell wall polysaccharide. J Infect Dis 1990; 161: 728-35.
14 Alho OP. The validity of questionnaire reports of a history of acute otitis media. Am...

...48: 356-63.
18 Kilpi T, Palmu A, Jokinen J, Kahty H, Makela. Efficacy of conjugate vaccine against acute otitis media (AOM)-Finnish Experience. In: Program and abstracts of the 3rd International Symposium on Pneumococci and Pneumococcal Diseases, Anchorage, May 5 -8, 2002: 110 (abstr).
19 Kalm O, Prellner K, Freijd A, Rynnel-Dagoo B. Antibody activity before and after pneumococcal vaccination of otitis-prone and non-otitis-prone children. Acta Otolaryngol 1986; 101: 467-74...

...Dagan R, Givon-Lavi N, Zamir O, et al. Reduction of nasopharyngeal carriage of Streptococcus pneumoniae after administration of a 9-valent pneumococcal conjugate vaccine to toddlers attending day care centers. J Infect Dis 2002 ; 185: 927-36.
21 Syrjanen RK, Kilpi TM, Kaijalainen TH, Herva EE, Takala AK. Nasopharyngeal carriage of Streptococcus pneumoniae in Finnish Children younger than 2 years old. J Infect Dis 2001; 184: 451-59.
22 Obaro SK, Adegbola RA, Banya WA, Greenwood BM. Carriage of pneumococci after pneumococcal vaccination. Lancet 1996; 348: 271-72.
23 Dagan R, Sikuler-Cohen M, Zamir O, Janco J, Givon-Lavi N, Fraser D. Effect of conjugate pneumococcal vaccine on the occurrence of respiratory infections and antibiotic use in day-care center attendees...
...Dykes JK, Johnson SE, Ades EW, King J, Briles DE, Carlone GM. Competition among Streptococcus pneumoniae for intranasal colonization in a mouse model. Vaccine 2000; 18: 2895-901.
25 Spratt BG, Greenwood BM. Prevention of pneumococcal disease by vaccination: does serotype replacement matter? Lancet 2000; 356: 1210-11.
26 Douglas RM, Miles HB. Vaccination against Streptococcus pneumoniae in childhood: lack of demonstrable benefit in young Australian children. J Infect Dis 1984; 149...

...C, Christensen P, Hovelius B, Prellner K. A longitudinal study of the nasopharyngeal carriage of pneumococci as related to pneumococcal vaccination in children attending day-care centres. Acta Otolaryngol 1984; 98: 524-32.
28 Faden...

...1997; 175:1140-45.
29 Gray BM, Converse GM, Dillon HC. Epidemiologie Studies of Streptococcus pneumoniae in infants: acquisition, carriage, and infection during the first months of life. J Infect Dis...

04210365 SUPPLIER NUMBER: 199461169 (USE FORMAT 7 OR 9 FOR FULL TEXT
)
13-valent PCV poised to replace 7-valent.(INFECTIOUS DISEASES)
Tucker, Miriam E.
Family Practice News, 39, 8, 17(1)
April 15,
2009
PUBLICATION FORMAT: Magazine/Journal ISSN: 0300-7073 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 455 LINE COUNT: 00037

TEXT:
...from routine childhood immunization with the 7-valent Prevnar to use of a 13-valent pneumococcal conjugate vaccine that is still under investigation.
... 13-valent version contains the same amounts of the same seven serotypes that Prevnar has (4, 6B, 9V,, 14, 18C, 19F, and 23F) along with six new strains (1, 3, 5, 6A, 7F, and 19A). Each of these polysaccharides in both vaccines is conjugated to the same carrier protein, CRM197, he noted.

Since the introduction of Prevnar in 2000, the proportion of cases of invasive pneumococcal disease (IPD) caused by the seven vaccine strains has declined dramatically, while the proportion caused by other strains--19A in particular--has risen.

Dr. Paradiso summarized previously reported data from a pivotal trial done in Germany in which 603 infants received either PCV7 or PCV13 at 2, 3, and 4 months of age. The 13-valent version was noninferior against each serotype, while provoking a high antibody response rate to each of the six new serotypes.

Wyeth...

...than 90% of children aged 12 months and older, any child who received the primary 3-dose series with PCV7 could simply receive PCV13 as a booster after the age of...

...The company will first seek an indication for the use of PCV13 in children under 5 years old. It then hopes to bring it to adults over age 50, and ultimately...

DESCRIPTORS: Pneumococcal vaccine...

...Pneumococcal vaccine

14/3,K/29 (Item 2 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

04114369 SUPPLIER NUMBER: 196440259 (USE FORMAT 7 OR 9 FOR FULL TEXT
)
13-valent PCV poised to replace 7-valent version.(INFECTIOUS DISEASES)
Tucker, Miriam E.
Pediatric News, 43, 3, 10(1)
March,
2009
PUBLICATION FORMAT: Magazine/Journal ISSN: 0031-398X LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 696 LINE COUNT: 00055

TEXT:

...from routine childhood immunization with the 7-valent Prevnar to use of a 13-valent pneumococcal conjugate vaccine that is still under investigation.
... 13-relent version contains the same amounts of the same seven serotypes that Prevnar has (4, 6B, 9V, 14, 18C, 19F, and 23F) along with six new strains (1, 3, 5, 6A, 7F, and 19A). Each of these polysaccharides in both vaccines is conjugated to the same carrier protein, CRM197, using the same conjugation chemistry. "So, PCV13 uses a technology that has worked successfully with Prevnar," he noted.

Since the introduction of Prevnar in 2000, the proportion of cases of invasive pneumococcal disease (IPD) caused by the seven vaccine strains has declined dramatically, while the proportion due to other strains--19A in particular has risen. In 2006, the proportion of IPD cases caused by the seven strains included in Prevnar was 2% in children aged younger than 2 years and 4% in those aged 2-4 years. In contrast, the proportion of IPD cases caused by the 13 serotypes in the new version was 64% and 73%, respectively, with half of the cases due to 19A.

(ILLUSTRATION OMITTED)

Dr. Paradiso summarized previously reported data from a pivotal trial done in Germany in which 603 infants were randomized to receive either PCV7 or PCV13 at 2, 3, and 4 months of age. The 13-valent version was noninferior against each serotype, while provoking a high antibody response rate to each of the six new serotypes. The...

...safety profile of PCV13 was comparable with that of PCV7 in a database that includes 4,783 PCV13 recipients in a total study population of 7,240, he said. Wyeth's...

...of Alaska to test the safety and effectiveness of this scheme in children younger than 5 years old, he said.

The company will first seek an indication for the use of PCV13 in children younger than 5 years old. After that, it hopes to bring it to adults over age 50, and...

14/3,K/30 (Item 3 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

03974608 SUPPLIER NUMBER: 191426768 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Added strains give PCV13 promising results in Europe: serotype 19A immunogenicity was high.(News)
Splete, Heidi
Pediatric News, 42, 12, 1(2)
Dec,
2008
PUBLICATION FORMAT: Magazine/Journal ISSN: 0031-398X LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 1268 LINE COUNT: 00104

Added strains give PCV13 promising results in Europe: serotype 19A immunogenicity was high.(News)

TEXT:

WASHINGTON -- An updated pneumococcal conjugate vaccine containing 13 different bacterial strains appears to be safe and immunogenic, based on pilot...
... and Chemotherapy and the annual meeting of the Infectious Diseases Society of America.

"Globally, the pneumococcus has been estimated to account for

around 1 million deaths annually in children less than 5 years old," wrote Dr. Dorothee Kieninger of Johannes Gutenberg University in Mainz, Germany, and colleagues...

...the Centers for Disease Control and Prevention in Atlanta have shown a significant decrease in pneumococcal disease in children in the United States thanks to the 7-valent pneumococcal conjugate vaccine (PCV7). But outbreaks of disease in recent years have been linked to bacterial strains not included in this vaccine, particularly serotype 19A, according to the CDC.

The studies presented at the meeting showed that the new vaccine...

...receive PCV7 (303 infants) or the new vaccine PCV13 (301 infants). The children received the pneumococcal vaccines in addition to a combined diphtheria, tetanus, and acellular pertussis (DTaP) vaccine, inactivated polio...

...hepatitis B surface antigen (HBsAg) (GlaxoSmithKline's Infanrix hexa). They received the vaccinations at 2, 3, and 4 months, and again at 11-12 months. Blood samples were taken after the infant series at 5 months, and again after the toddler vaccination at 12-13 months.

The researchers compared adverse events and assessed immune responses to the seven serotypes in PCV7 (4, 6B, 9V, 14, 18C, 19F, and 23F) and the six additional strains in PCV13 (1, 3, 5, 6A, 7F, and 19A).

Overall, antibody responses to the PCV7 serotypes were similar in both groups. But for the...

...higher in the PCV13 group, compared with the PCV7 group.

The positive antibody response of 19A is of particular interest, given the increased incidence of pneumococcal disease caused by this serotype, Dr. Christine Juergens of Wyeth Research in Muenster, Germany, said in an interview.

The primary...

...who achieved an antipolysaccharide IgG binding concentration of at least 0.35 mcg/mL. For 19A, this percentage was 99% in the PCV13 group.

The lack of interference from concomitant vaccines...

...randomized to receive PCV13 and 263 who received PCV7.

The infants were vaccinated at 2, 3, and 4 months of age, and blood samples were taken at 5 months to measure immune response.

After dose 3 of the infant series, the pneumococcal immune response rate in the PCV13 group was at least 72% for all serotypes and 98% for 19A. Antibody response rates to the concomitant vaccine ranged from 59% to 100% in the PCV13...

...University of Oxford (England), and colleagues. This study included data from 135 infants aged 6-14 weeks who were randomized to receive PCV13 and 132 infants who received PCV7. Infants in both groups received the meningococcal serotype C vaccine at 2 and 4 months of age, and the pneumococcal conjugate vaccine, plus a DTaP, IPV, and Hib vaccine at age 2, 3, and 4 months.

Overall, 79%-96% of the children who received PCV13 met the criteria for protection...

...the six serotypes not included in PCV7, and 95% met the criteria for protection against 19A. "PCV13 was immunogenic and well tolerated when given as part of the UK infant vaccine...

...DTaP, IPV, Hib vaccine, and a hepatitis B vaccine. The infants were vaccinated at 2, 3, and 4 months of age, and the researchers took blood samples at 5 months to test for immune response.

Overall, the proportions of responders who met the criteria for immunogenicity and geometric mean concentration were similar in both groups. For serotype 19A, both groups achieved identical response rates of 99%.

Adverse events were mostly mild or moderate...

...conclusion that PCV13, in its final manufacturing scale and formulation, will be effective in preventing pneumococcal disease caused by the vaccine serotypes," the researchers wrote.

All four studies were supported by...

14/3,K/31 (Item 4 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

03942219 SUPPLIER NUMBER: 190747139 (USE FORMAT 7 OR 9 FOR FULL TEXT)
PCV13 is promising against worrisome serotypes.(Infectious Diseases)(pneumococcal conjugate vaccineS)
Splete, Heidi
Family Practice News, 38, 22, 14(2)
Nov 15, 2008
PUBLICATION FORMAT: Magazine/Journal ISSN: 0300-7073 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 1224 LINE COUNT: 00100

PCV13 is promising against worrisome serotypes.(Infectious Diseases)(pneumococcal conjugate vaccineS)

TEXT:

WASHINGTON -- An updated pneumococcal conjugate vaccine containing 13 different bacterial strains appears to be safe and immunogenic, based on pilot...

... ICAAC) and the annual meeting of the Infectious Diseases Society of America (IDSA).

"Globally, the pneumococcus has been estimated to account for around 1 million deaths annually in children less than 5 years old," stated Dr. Dorothee Kieninger of Johannes Gutenberg University in Mainz, Germany, and colleagues...

...the Centers for Disease Control and Prevention in Atlanta have shown a significant decrease in pneumococcal disease in U.S. children thanks to the 7-valent pneumococcal conjugate vaccine (PCV7). But outbreaks of disease in recent years have been linked to bacterial strains not included in this vaccine, particularly serotype 19A, according to the CDC.

The studies presented at the meeting showed that the new vaccine...

...receive PCV7 (303 infants) or the new vaccine PCV13 (301 infants). The children received the pneumococcal vaccines in addition to a combined diphtheria, tetanus, and acellular pertussis (DTaP) vaccine, inactivated polio...

...hepatitis B surface antigen (HBsAg) (GlaxoSmithKline's Infanrix hexa). They received the vaccinations at 2, 3, and 4 months, and again at 11-12 months. Blood samples were taken after the infant series at 5 months, and again after the toddler vaccination at 12-13 months.

The researchers compared adverse events and assessed immune responses to the seven serotypes in PCV7 (4, 6B, 9V, 14, 18C, 19F, and 23F) and the six additional strains in PCV13 (1, 3, 5, 6A, 7F, and 19A).

Overall, antibody responses to the PCV7 serotypes were similar in both groups. But for the...

...higher in the PCV13 group, compared with the PCV7 group.
The positive antibody response of 19A is of particular interest, given the increased incidence of pneumococcal disease caused by this serotype, Dr. Christine Juergens of Wyeth Research in Muenster, Germany, said in an interview.
The primary...

...who achieved an antipolysaccharide IgG binding concentration of at least 0.35 mcg/mL. For 19A, this percentage was 99% in the PCV13 group.
The lack of interference from concomitant vaccines...

...randomized to receive PCV13 and 263 who received PCVT. The infants were vaccinated at 2, 3, and 4 months of age, and blood samples were taken at 5 months to measure immune response.
After dose 3 of the infant series, the pneumococcal immune response rate in the PCV13 group was at least 72% for all serotypes and 98% for 19A. Antibody response rates to the concomitant vaccine ranged from 59% to 100% in the PCV13...

...University of Oxford (England), and colleagues. This study included data from 135 infants aged 6-14 weeks who were randomized to receive PCV13 and 132 infants who received PCV7. Infants in both groups received the meningococcal serotype C vaccine at 2 and 4 months of age, and the pneumococcal conjugate vaccine, plus a DTaR IPV, and Hib vaccine at age 2, 3, and 4 months.
Overall, 79%-96% of the children who received PCV13 met the criteria for protection...

...the six serotypes not included in PCV7, and 95% met the criteria for protection against 19A. "PCV13 was immunogenic and well tolerated when given as part of the UK infant vaccine...

...DTaP, IPV, Hib vaccine, and a hepatitis B vaccine. The infants were vaccinated at 2, 3, and 4 months of age, and the researchers took blood samples at 5 months to test for immune response.
Overall, the proportions of responders who met the criteria for immunogenicity and geometric mean concentration were similar in both groups. For serotype 19A, both groups achieved identical response rates of 99%.
Adverse events were mostly mild or moderate...

DESCRIPTORS: Pneumococcal vaccine...

14/3,K/32 (Item 5 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

03823739 SUPPLIER NUMBER: 185210251 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Pediatric parapneumonic empyema, Spain.(RESEARCH)
Obando, Ignacio; Munoz-Almagro, Carmen; Arroyo, Luis A.; Tarrago, David; Sanchez-Tatay, David; Moreno-Perez, David; Dhillon, Sahar S.; Esteva, Cristina; Hernandez-Bou, Susanna; Garcia-Garcia, Juan J.; Hausdorff, William P.; Brueggemann, Angela B.
Emerging Infectious Diseases, 14, 9, 1390(8)
Sept,
2008
PUBLICATION FORMAT: Magazine/Journal ISSN: 1080-6040 LANGUAGE: English

RECORD TYPE: Fulltext TARGET AUDIENCE: Academic; Professional
WORD COUNT: 5124 LINE COUNT: 00569

TEXT:

Pediatric parapneumonic empyema (PPE) has been increasing in several countries including Spain. Streptococcus pneumoniae is a major PPE pathogen; however, antimicrobial pretreatment before pleural fluid (PF) sampling frequently results in negative diagnostic cultures, thus greatly underestimating the contribution of pneumococci, especially pneumococci susceptible to antimicrobial agents, to PPE. The study aim was to identify the serotypes and...

...total of 208 children with PPE were prospectively enrolled; blood and PF samples were collected. Pneumococci were detected in 79% of culture-positive and 84% of culture-negative samples. All pneumococci were genotyped by multilocus sequence typing. Serotypes were determined for 111 PPE cases; 48% were serotype 1, of 3 major genotypes previously circulating in Spain. Variance in patient complication rates was statistically significant by serotype. The recent PPE increase is principally due to nonvaccine serotypes, especially the highly invasive serotype 1.

****

Pleural effusions occur in at least 40% of children hospitalized with bacterial pneumonia. Occasionally, the infectious agent invades the pleura to cause pediatric paraneumonic empyema (PPE) (1), characterized by the presence of pus. Although rarely associated with fatalities in industrialized countries, PPE...

...and surgical intervention, and patients are at risk for serious and long-lasting illness (2,3).

An increasing incidence of PPE has been reported in several countries since the mid-1990s (2-6), but it is not clear why. Streptococcus pneumoniae is the most frequently found microorganism in most recent reports. However, conventional microbiologic culture methods...

...samples (7), can be useful adjuncts in defining the contributory role of different microorganisms and pneumococcal serotypes to PPE etiology (4, 8).

Our study's goal was to prospectively investigate the molecular epidemiology of pneumococcal PPE among children admitted to 3 of the largest tertiary-care pediatric hospitals in Spain. There were 4 objectives: 1) identify the serotypes and multilocus sequence typing (MLST) genotypes causing PPE and determine whether a...

...determine whether the causal genotypes were only associated with PPE or also caused other invasive pneumococcal disease (IPD) in the same population, or were carried by healthy children; 3) compare serotypes and genotypes recovered from northern and southern Spain in the context of regional differences in 7-valent pneumococcal conjugate vaccine (PCV7) uptake; and 4) identify any differences between highly invasive serotypes and more opportunistic serotypes with respect to epidemiology...

...of age at Sant Joan de Deu Hospital Barcelona, Spain, were prospectively enrolled beginning October 1, 2003. PPE patients <14 years of age admitted to Virgen del Rocio Children's Hospital (VRCH) in Seville and Carlos de Haya Children's Hospital (CHCH) in Malaga were prospectively enrolled beginning January 1, 2005. The study period extended to June 30, 2006, in all locations for molecular analyses...

...notification by attending physicians or by clinical microbiology laboratories when a sterile site sample was pneumococcal culture or pneumolysin (ply) positive. Participating centers served a pediatric

referral population of 607,796 (9% of the...

...swab specimens were obtained from 635 children 6 months to 6 years of age attending 4 primary healthcare centers for well-child visits and 2 hospital emergency rooms in Seville. Exclusion...

...retrospectively ascertained from microbiology department databases of both centers and confirmed by chart review. Viable pneumococcal isolates were serotyped (70% of cases) by the Spanish Reference Laboratory of Pneumococci and genotyped by MLST (61% of cases).

Testing of PF Samples

Pneumococci were identified by using microbiologic and molecular genotyping methods; susceptibility testing was performed by agar ...

...used to define susceptibility (10). Culture-negative PFs were assayed for the presence of the pneumolysin (ply) gene, by using a real-time PCR in Barcelona adapted from Corless et al...

...Mountain View, CA, USA) in Seville.

Molecular Genotyping

MLST was performed by using standard methods (14), with the exception of a change in PCR primers for the gdh, recP, xpt genes...

...www.mlst.net).

Statistical Analyses

Statistical analyses were performed by using SPSS for Windows version 14.0 (SPSS, Inc., Chicago, IL, USA). Reported p values were 2-tailed, and the level...

...PPE Trends

In Seville and Malaga, the annual number of PPE cases increased 13-fold (5 to 66 cases) during 1998-2006 (Figure 1). In Barcelona, the annual number of PPE cases increased from 11 cases in 2004 to...

...no obvious changes in referral patterns, overall pediatric population, guidelines for evaluating children with fever, pneumonia or PPE, or recommendations for performing diagnostic thorachocentesis in children with PPE were found. Table 1 describes the demographic characteristics of the 208 PPE patients prospectively enrolled during the molecular analysis ...

...seven (32%) patients had positive blood and/or PF cultures for any pathogen, and S. pneumoniae was isolated from 53 (79%) of these cases (Figure 2). In 51 of these, a pneumococcal serotype could be identified via the conventional Quellung reaction. Evidence of pneumococcal infection in 99 (84%) of 118 culture-negative PF samples was found on the basis...

...likely to have received antimicrobial drug therapy before PF aspiration than patients with culture-positive pneumococcal PPE (92% vs. 53%; $p<0.0001$). Of the 99 culture-negative PF samples, 67...

...positive/wzg-positive and 2 ply-negative/wzg-positive) had a sufficient sample to enable serotype testing by PCR. In 52 of these samples, a serotype could be identified. Thus, a pneumococcal serotype was identified in 103 PF samples (Figure 2).

In addition, a predicted serotype based on MLST genotyping was established for 2 cases with negative PCR results and 6...

...was possible (Figure 2). Such predictions were possible because there is a strong relationship between serotype and MLST genotype for most genotypes (16-18; www.mlst.net), with the exception of a small number of

well-known genotypes that are associated with different serotype variations.

Eighty-one PF samples were fully genotyped, and 18 were partially genotyped ((greater than or equal to) 4 alleles), by MLST. An ST was identified for 31 of the 99 culture-negative/ply...

...predicted serotypes (Figure 2). Eighteen PF samples were partially genotyped by MLST: 2 were presumptive serotype 1 pneumococci based on 5-6 loci matching ST228; 1 was a presumptive serotype 5 based on 5 loci matching ST1223; 7 were genotyped at (greater than or equal to) 4 loci and serotyped by PCR (serotype 1, n = 5; serotype 7F and 19A, n = 1 each); and 8 samples were partially genotyped at (greater than or equal to) 4 loci (indicating presence of a pneumococcus), but PCR serotyping was either negative or not performed. Samples with predicted serotypes based on incomplete genotyping data were not included in further analyses.

(FIGURE 1 OMITTED)

Serotype Distribution

Ten serotypes were identified among the 111 PPE cases with tentatively assigned or confirmed serotyping information (Table 2). Non-PCV7 serotypes caused 96 (89%) cases of PPE, including serotype 1, which was detected in 48% of the patient samples. Although a significantly higher proportion of PPE was caused by 7F in Seville and Malaga than in Barcelona, the contribution of other serotypes by region was...

...005), but there were no significant regional differences in vaccination status among children infected with serotype 1 (28% vs. 22%, p = 0.63).

(FIGURE 2 OMITTED)

Eight (15%) of 53 cultured pneumococci were intermediately penicillin resistant and 4 (8%) were resistant at high levels. Serotype 1, 3, 5, and 7F pneumococci were uniformly susceptible to penicillin and significantly more common among culture-negative than culture-positive...

...Genotyping by MLST

Eighty-one PF samples were fully genotyped; 26 STs were identified (Table 3). Three of the major serotype 1 STs (18), ST228, ST304 and ST306, were identified, although ST228 was only detected in Seville and Malaga, and ST304 only in Barcelona (Table 3). Serotypes 5 and 7F were represented by globally distributed genotypes ST289 ((Colombia.sup.5)-19) and a closely related single-locus variant, ST1223; and ST191 ((Netherlands.sup.7F)-39), respectively.

Six of 7 serotype 14-positive PF samples were ST156 ((Spain.sup.9V)-3). Genotypic diversity among the serotypes in this study was greatest for serotype 19A; 5 unrelated STs were detected, including ST81 ((Spain.sup.23F)-1). Such variants of ST81 have also previously been detected.

IPD and Nasopharyngeal Carriage in Seville and Malaga

During 2001-2006, 180 cases of IPD involving children <14 years of age were diagnosed with IPD at Seville and Malaga hospitals, and 126 isolates...

...isolates were also genotyped. Twenty-three percent (29/126) of all IPD was due to serotype 1. Over this period, there was a statistically nonsignificant increase in the proportion of IPD cases due to serotype 1:17% (2001-2003) vs. 27% (2004-2006), p = 0.19.

Twenty-four serotypes were identified; 10 serotypes caused both PPE and other IPDs (Table 4), and 14 serotypes caused only other IPDs (6B, 11, 13, 15A, 16, 18C, 22, 23A, 23B, 23F, 24, 33, 34, and 38). Serotype 1 isolates were almost exclusively

associated with pulmonary disease, including bacteremic pneumonia (12/29, 41%) and PPE (15/29, 52%). The 3 major serotype 1 PPE genotypes were also found among this collection of serotype 1 IPD isolates, although ST304 was no longer detected after 2002 and ST306 was first detected in 2003. A retrospective analysis of serotype 1 invasive isolates submitted to the Spanish National Reference Laboratory since 1990 showed ongoing circulation of ST228 and ST304, but ST306 was only detected once before 2000 (1998; unpub, data).

Serotype 14 was the second most common IPD-causing serotype, with an overall prevalence of 17% (23% in 2001-2003 and 12% in 2004-2006; p = 0.12). The major serotype 14 genotype (ST156) identified in PF samples was also detected throughout the entire 2001-2006 period among carriage isolates and in culture-positive IPD cases, mainly causing pulmonary disease (Table 4). Ten (8%) cases of culture-positive IPD were due to serotype 7F, 9 of which were detected after 2004. ST191 was the only serotype 7F genotype in IPD and NP carriage.

Serotype-Specific Differences in Clinical Epidemiology, Inflammatory Markers, and Outcome

PPE-associated serotypes were divided into 3 groups: 1) serotypes 1, 5, 7F, and 14, consistently associated with the highest estimates of serotype-specific high invasive disease potential (HIDP) (16,17,19); 2) serotype 3 alone; and 3) serotypes 6A, 9V, 19A, and 23F, which have a low invasive disease potential (LIDP) (16,17,19). Odds ratio estimates of...

...disease potential demonstrate as much as 60- to 120-fold variation between the most invasive (1, 4, 5, 7, 14, 18C) and the least invasive (3, 6A, 15, 23F) serotypes/serogroups (16,19).

PPE cases with HIDP serotypes were older than those with LIDP serotypes (median ages 56 and 24 months, respectively; p = 0.0001) (Table 5). Among HIDP PPE cases, 74% were due to serotypes 1 (n = 53) and 5 (n = 9) and comprised children >36 months of age, whereas serotype 14 (n = 9) only caused PPE in patients <36 months of age (data not shown; p = 0.0001). Serotype 3 PPE was associated with significantly more complications than PPE caused by HIDP and LIDP serotypes combined (p = 0.004). No other characteristics differed significantly between individual groups (Table 5).

Discussion

In this study, we used molecular techniques to sensitively evaluate PPE epidemiology among a large number of patients in geographically diverse locations of Spain. There was evidence of pneumococcal infection in most of the culture-positive and culture-negative cases of PPE, which was mainly associated with nonvaccine serotype 1 followed by 3, 5, 7F, and 19A, as well as vaccine serotype 14. Serotypes 1, 3, and 14 in particular are well-known PPE-associated serotypes (2,4,7,20,21). Antimicrobial drug-susceptible serotypes 1, 3, 5, and 7F were overrepresented in culture-negative PF samples, pointing to an important potential bias in PPE surveillance when surveillance is based solely on conventional microbiologic culture methods. Infection with serotype 3 was a risk factor independently associated with PPE complications, a finding also seen in a US study (22).

Serotype 1 has also been the most prevalent IPD serotype among Spanish children <14 years of age, representing 5%, 11%, and 27% of all culture-positive pediatric IPD isolates sent to the Pneumococcal Reference Laboratory in 1997, 2003, and 2006, respectively (23). However, the increase in serotype 1 disease cannot easily be explained by a vaccine effect, in part because PCV7 coverage was...

...34%-45% in 2004-2005 (24,25).

In addition, increased PPE incidence largely caused by serotype 1 was reported in the United States and the United Kingdom in the decades before PCV7 introduction in 2000 and late 2006, respectively (4,6,20). Previous studies have suggested that the high year-to-year variability of serotype 1 and 5 disease may represent large-scale outbreaks of a cyclical nature (26-28).

However, the observation in this study that 2 of the 3 MLST genotypes of serotype 1 (ST228 and ST304) had been "resident" in Spain at least since 1990 indicates that serotype 1 PPE increases in Spain were likely not due to a recent introduction of a specific...

...In general, MLST analyses demonstrated that the recent increase in PPE was mainly due to pneumococcal STs previously described to be present in Spain and other European countries for some years...

...not enable a longer-term analysis of PPE epidemiology. Second, our analyses relied exclusively on serotype identification and MLST genotyping, neither of which detects differences in virulence factors apart from the serotype. Genetic factors independent of the capsule have been associated with invasiveness and disease severity (17...
...come from parent reporting. Finally, the results obtained here may not apply to less severe pneumonia cases, whose etiology may be qualitatively different.

Unfortunately, PCV7 has a serotype coverage of only 11%-14% (including the cross-reactive 6A) in the population of PPE patients. However, conjugate vaccines containing serotypes 1, 5, and 7F, such as the newly developed 10-valent pneumococcal Haemophilus influenzae protein D conjugate vaccine candidate (35), could increase the serotype coverage for PPE up to 80%; the subsequent addition of serotypes 3 and 19A in vaccine candidates currently in development would add an additional 18% of coverage (35). Finally...

...This research was supported by Fondo de Investigaciones Sanitarias (PI050924 and CP05/00068), the Spanish Pneumococcal Infection Study Network (G03-103) and the Spanish Network for the Research in Infectious Diseases...

...and D.S.-T. was supported by Consejeria de Salud from the Andalusian Government.

References

(1.) Chonmaitree T, Powell KR. Parapneumonic pleural effusion and empyema in children. Review of a 19...

...Barson W J, Schutze GE, Bradley JS, et al. Clinical characteristics of children with complicated pneumonia caused by Streptococcus pneumoniae. Pediatrics. 2002;110:1-6. DOI: 10.1542/peds.110.1.1

(3.) Hsieh YC, Hsueh PR, Lu CY, Lee PI, Lee CY, Huang LM. Clinical manifestations and molecular epidemiology of necrotizing pneumonia and empyema caused by Streptococcus pneumoniae in children in Taiwan. Clin Infect Dis. 2004;38:830-5. DOI: 10.1086/381974

(4.) Eastham KM, Freeman R, Kearns AM, Eltringham G, Clark J, Leeming J, et al. Clinical...

...outcome of empyema in children in the north east of England. Thorax. 2004;59:522-5. DOI: 10.1136/thx.2003.016105

(5.) Deiros Bronte L, Baquero-Artigao F, Garcia-Miguel M J, Hernandez Gonzalez N, Pena Garcia...

...Martin F. Parapneumonic pleural effusion: an 11-year review. An Pediatr

(Barc). 2006;64:40-5. DOI: 10.1157/13083830
(6.) Byington CL, Spencer LY, Johnson TA, Pavia AT, Allen D...
...I, Arroyo L, Sfinchez Tatay D, Moreno D, Hausdorff WP, Brueggemann AB. Molecular typing of pneumococci causing parapneumonic empyema in Spanish children using multilocus sequence typing directly on pleural fluid samples. Pediatr Infect Dis J. 2006;25:962-3. DOI: 10.1097/01.inf.0000235684.89728.38
(8.) Le Monnier A, Carbolmelle E, Zahar...

...al. Microbiologic diagnosis of empyema in children: comparative evaluations by culture, polymerase chain reaction, and pneumococcal antigen detection in pleural fluids. Clin Infect Dis. 2006;42:1135a40. DOI: 10.1086/502680
(9.) O'Brien KL, Nohynek H; WHO Pneumococcal Vaccine Trials Carriage Working Group. Report from a WHO working group: standard method for detecting upper respiratory carriage of Streptococcus pneumoniae. Pediatr Infect Dis J. 2003;22:e1-11. DOI: 10.1097/00006454-200302000-00010
(10...

...V, Fox A J, Kaczmarski EB. Simultaneous detection of Neisseria meningitidis, Haemophilus influenzae, and Streptococcus pneumoniae in suspected cases of meningitis and septicemia using real-time PCR. J Clin Microbiol. 2001;39:1553-8. DOI: 10.1128/JCM.39.4.1553-1558.2001
(12.) Toikka P, Nikkari S, Ruuskanen O, Leinonen M, Mertsola J. Pneumolysin PCR-based diagnosis of invasive pneumococcal infection in children. J Clin Microbiol. 1999;37:633-7.
(13.) Tarrago D, Fenoll A, S/anchez-Tatay D, Arroyo LA, Munoz-Almagro C, Esteva C, et al. Identification of pneumococcal serotypes from culture-negative clinical specimens by novel real-time PCR. Clin Microbiol infect, in press.
(14.) Enright MC, Spratt BG. A multilocus sequence typing scheme for Streptococcus pneumoniae: identification of clones associated with serious invasive disease. Microbiology. 1998; 144:3049-60.
(15.) Enright...

...Griffiths, Meats E, Peto T, Crook DW, Spratt BG. Clonal relationships between invasive carriage Streptococcus pneumoniae and serotype - and clone-specific differences in invasive disease potential. J Infect Dis. 2003;187:1424-32...

...Olsson-Liljequist B, Christensson B, Samuelsson A, Kronvall G, et al. Effect of clonal and serotype-specific properties on the invasive capacity of Streptococcus pneumoniae. J Infect Dis. 2004;189:785-96. DOI: 10.1086/381686
(18.) Brueggemann AB, Spratt BG. Geographic distribution and clonal diversity of Streptococcus pneumoniae serotype 1 isolates. J Clin Microbiol. 2003;41:4966-70. DOI: 10.1128/JCM.41.11.49664970...

...KG, Spratt BG. Temporal and geographic stability of the serogroup-specific invasive potential of Streptococcus pneumoniae in children. J Infect Dis. 2004; 190:1203-11. DOI: 10.1086/423820
(20.) Byington CL, Korgenski K, Daly J, Ampofo K, Pavia A, Mason EO. Impact of the pneumococcal conjugate vaccine on pneumococcal parapneumonic empyema. Pediatr Infect Dis J. 2006;25:250a4. DOI: 10.1097/01 .inf.0000202137...

...Sardet A, de La Rocque F, Lecuyer A, et al. Multicenter pediatric retrospective study on pneumonia with empyema in France. Arch Pediatr. 2005;12:823-6. DOI: 10.1016/j.arcped.2005.04.024
(22.) Tan TQ; US Pediatric Multicenter Pneumococcal Surveillance Study Group. 5th International Symposium on Pneumococci and Pneumococcal Disease; Alice Springs, Northern Territory,

Australia; 2006 Apr 2-6.
(23.) Fenoll A, Tarrago D...

...Calbo E, Diaz A, Cafiadell E, Ffibrega J, Uriz S, Xercavins M, et al. Invasive pneumoeoccal disease among children in a health district of Barcelona: early impact of pneumococcal conjugate vaccine. Clin Microbiol Infect. 2006;12:867-72. DOI: 10.1111/j. 1469-0691 .2006.1502 1.x
(25.) Barricarte A, Castilla J, Gil-Setas A, Torroba L, Navarro-Alonso JA, Irisarri F, et al. Effectiveness of the 7-valent pneumococcal conjugate vaccine: a population-based case-control study. Clin Infect Dis. 2007;44:1436-41. DOI...

...S, Belmaker I, Porat N, Siton Y, Weber G, et al. An outbreak of Streptococcus pneumoniae serotype 1 in a closed community in southern Israel. Clin Infect Dis. 2000;30:319-21. DOI...

...Akerlund T, Liljequist BO, Hedlund J, et al. Dynamics of penicillin-susceptible clones in invasive pneumococcal disease. J Infect Dis. 2001;184:861 9. DOI: 10.1086/323339
(28.) HausdorffWP. The roles of pneumococcal serotypes 1 and 5 in paediatric invasive disease. Vaccine. 2007;25:2406-12. DOI: 10.1016/j. vaccine.2006...

...Fenoll A, Griffiths D, Spratt BG. The three major Spanish clones of penicillin-resistant Streptococcus pneumoniae are the most common clones recovered in recent cases of meningitis in Spain. J Clin...
...Sorberg M, Henriques Normark B, Kronwall G. Capsular types and antibiotic susceptibility of invasive Streptococcus pneumoniae among children in Sweden. Scand J Infect Dis. 2003;35:452-8. DOI: 10.1080/00365540310013315
(31.) UK Health Protection Agency. Pneumococcal serotype distribution for samples referred for serotyping epidemiological years (July-June): 2000/1a005/6 (cited 2007...

...Kalin M, Sandgren A, Kuhlmann-Berenzon S, et al. Clonal and capsular types decide whether pneumococci will act as a primary or opportunistic pathogen. Clin Infect Dis. 2006;42:451-9...

...Hinds J, Smith A, Clarke SC, et al. Genomic diversity between strains of the same serotype and multilocus sequence type among pneumococcal clinical isolates. Infect Immun. 2006;74:3513-8. DOI: 10.1128/IAI.00079-06
(34.) Watson M, Gilmour R, Menzies R, Ferson M, McIntyre P; New South Wales Pneumococcal Network. The association of respiratory viruses, temperature, and other climatic parameters with the incidence of invasive pneumococcal disease in Sydney, Australia. Clin Infect Dis. 2006;42:211-5. DOI: 10.1086/498897
(35.) Hausdorff WP, Brneggemann AB, Hackell J, Scott JAG. Pneumococcal serotype epidemiology. In: Siber GR, Klugman KP, Makela PH, editors. Pneumococcal vaccines: the impact of conjugate vaccines. Washington: ASM Press; 2008. p. 139-62.
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...interests include the epidemiology and treatment of pediatric infectious diseases with a special focus on pneumococcus and respiratory viruses.
Table 1. Demographic characteristics of 208 patients with PPE enrolled during the molecular analysis study period *

Characteristic...

...mo, mean (+ or -) SD (range) 51.8 (+ or -) 31 (2-180)

Gender ratio, M/F	1.06
Underlying disease, %((dagger))	4
Oral antimicrobial drugs before admission, %((double dagger))	29
Antimicrobial drug free before thoracocentesis, %((section))	23
PCV7 (greater than or equal to)1 dose, %	31
Referral, %	38

* PPE, pediatric parapneumonic empyema; PCV7, 7-valent pneumococcal conjugate vaccine.

...congenital heart disease (2), mild psychomotor retardation (2), varicella zoster infection (2) and genetic disease (1).

((double dagger)) Median duration: 3 d, range 1-17 d.

((section)) 100/147 children who had not been treated with oral antimicrobial drug...

...admission received intravenous antimicrobial drug treatment before thoracocentesis for a median of 2 d (range 1-10 d).

Table 2 Pneumococcal serotypes identified among pleural fluid samples

Serotype *	Barcelona, no. (%), n = 56	Seville/Malaya, no. n = 55
1	27 (48)	26 (47)
7F	3 (5)	11 (20)
3	5 (9)	7 (13)
5	6 (11)	3 (5)
14	4 (7)	5 (9)
19A	6 (11)	2 (4)
9V	2 (4)	0
6A	2 (4)	0
8	0	1 (2)
19F	1 (2)	0

Serotype *	Total, no. (%), n = 111	p value
1	53 (48)	0.92
7F	14 (13)	0.02
3	12 (11)	0.56
5	9 (8)	0.28
14	9 (8)	0.74
19A	8 (7)	0.27
9V	2 (2)	0.50
6A	2 (2)	0.50
8	1 (0.9)	1
19F	1 (0.90	1

* 7-valent pneumococcal conjugate vaccine serotypes include 4, 6B, 9V, 14, 18C, 19F, 23F

. Pleural fluid samples were collected in Barcelona from October 1, 2003, through June 30, 2006, and in Seville and Malaga from January 1, 2005, through June 20, 2006. Serotypes were determined by Quellung reaction or PCR testing or...

...multilocus sequence typing, as described in the text. Boldface represents a statistically significant result.

Table 3. Sequence types and serotypes among 81 pneumococci detected in pleural fluid

Serotyiae *	Total	Sequence type (n)
1	43	(306.sub.and SLVs) (23)((dagger)), 228 (11), (1), (304.sub.and SLVs) (8)((dagger))((section)), 2373 (1)
5	9	(289.sub.and SLVs) (9)((dagger))
3	8	180 (5), 260 (2), 2590 (1)((section))
14	7	156 (6), 17 (1)((section))
19A	6	276 (2), 81 (1)((section)), 202 (1)((section)), 1201 (1)((double dagger)), 2013 (1)((section))
7F	4	191 (4)
6A	2	135 (1)((double dagger)), 2377 (1)((section))
9V	2	838 (2)((section))

*Included are 8 strains that were culture and PCR negative, or not serotyped, but whose full genotyping by multilocus sequence typing (www.mist.net) enabled serotypes 1, 5, and 7F to be predicted. These serotypes were predicted because in each case the sequence type (ST) was identical or closely related to a known genotype for serotypes 1, 5 or 7F that have never been identified with anything other than those respective serotypes. These included ST (no.): 306 (2), 228 (1), 2373 (1), 2378 (1), 2561 (1), 1223 (1), and 191 (1).

((dagger)) SLV, single locus variant (i.e., differs at only 1 MLST locus and thus is a closely related genotype). Major serotypes 1 and 5 ST groups included (no. strains): ST306 (18) and SLVs 2375, 2376, 2378, and 2561 (1 each); ST304 (5) and SLVs 2374 (2), 2371 (1); ST289 (5), and SLV 1223 (4).

((double dagger)) Recovered only in Sevilla/Malaga.

((section)) Recovered only in Barcelona.

Table 4

. Contribution of PPE-associated serotypes and STs to IPD, Seville and Malaga, 2001-2006, and...

...6 years of aye, Seville * ((dagger))

Serotype	NO. (%) patients with IPD, n = 126	STs detected: diseases detected (no. patients), n = 111
1	29 (32)	228: P (7), PPE (6), A (1), B (1) 306 ((double dagger)): PPE (7), P (3) 304 ((section)): PPE (1)
14	22 (17)	156: P (7), PPE (4), M (2) 9: PPE (1) 62: P (1) 124: PPE (1) 2204: M (1)
7F	10 (8)	191: PPE (4), P (3), M (1), B (1)
19A	10 (8)	276: PPE (2), M (2), P (1) 202: B (1) 1201: PPE (1)
3	6 (5)	260: PPE (1), P (1), M (1) 180: PPE (1)
6A	5 (4)	1150: M (1) 1668: S (1) 1876: M (1)
5	3 (2)	289: PPE (2) 1223: P (1)
19F	3 (2)	87: C (1), B (1) 88:M(1)
9V	1 (1)	838: B (1)
8	1 (1)	53: M (1)

Serotype	Carriage, no. (%) patients, n = 194	STs detected in carriage (no. patients)	OR (95% CI)
1	1 (1)	306 (1)	57.7 (7.7-429.9)
14	15 (8)	156 (12)	2.5 (1.3-5.1)

		409 (1)	
		1684 (1)	
		2607 (1)	
7F	3 (2)	191 (3)	5.5 (1.5-20.3)
19A	13 (7)	276 (2)	1.2 (0.5-2.8)
		202 (3)	
		1201 (1)	
		199 (2)	
		433 (2)	
		392 (1)	
		2109 (1)	
		2609 (1)	
3	7 (4)	180 (3)	1.6 (0.5-4.6)
		260 (2)	
		2200 (2)	
6A	24 (12)	338 (8)	0.29 (0.1-0.79)
		386 (5)	
		1876 (3)	
		224 (2)	
		327 (1)	
		392 (1)	
		448 (1)	
		473 (1)	
		2201 (1)	
		2611 (1)	
5	2 (1)	289 (1)	2.3 (0.39-14.2)
		1540 (1)	
19F	8 (4)	81 (3)	0.57 (0.15-2.2)
		87 (1)	
		179 (2)	
		63 (1)	
		2615 (1)	
9V	3 (2)	838 (3)	0.5 (0.05-5)
8	0		--

* Culture-positive isolates only for IPD. Boldface indicates a statistically significant result and...

...the study period in Seville, Malaga, and Barcelona. An OR demonstrating the potential for each serotype to cause invasive disease, relative to its prevalence in nasopharyngeal carriage, was also calculated (16). Serotypes 6A, 19F, and 9V were associated with PPE in Barcelona (but not Seville and Malaga) and are included here for a complete list of invasive serotypes with any association to PPE among the 3 locations; however, data presented here are only from Seville and Malaga. Serotypes identified in IPD cases but not

among children with PPE: 6B, 11, 13, 15A, 16, 18C
, 22, 23A, 23B,
23F, 24, 33, 34, 38.

((dagger)) PPE, pediatric parapneumonic empyema; IPD, invasive pneumococcal disease; ST, sequence type; OR, odds ratio; CI, confidence interval; A, arthritis; B, occult bacteremia; P, pneumonia; M, meningitis; S, sepsis; C, orbital cellulitis.

((double dagger)) First detected in 2003.

((section)) First detected in 2002.

Table 5. Characteristics of children hospitalized with PPE, by serotype category, excluding patients with serious underlying disease (n=3) *

Characteristic	HIDP serotyhes, n = 84	Serotype 3, n = 11
Median age, mo (range)	55.6 (2-180)	37.9 (9-71)
Median hospital stay, ((double dager)) d (range)	13 (4-38)	15 (9-29)
Complications, % patients ((paragraph))	10	45

Characteristic...	LIDP

...pediatric parapneumic empyema; HIDP, high invasive disease potential; LIDP, low invasive disease potential. HIDP serotypes:
1,
5, 7F, and 14; LIDP serotypes: 6A, 9V,
19A, and 19F (16,17,19).
All results shown were statistically significant (p<0.05). There...

...mean lactate dehydrogenase; median days to thorachocentesis; referral; primary fibrinolytics or thoracoscopy; or oxygen requirement >4 d.

((dagger)) HIDP was compared with LIDP by post hoc analysis.

((double dagger)) Since being...

...significant differences between individual groups by post hoc analysis (p = 0.023 for comparison between serotype
3 and
LIDP)

((paragraph)) Complications included (no. patients): bronchopleural fistula (3), pyopneumothorax (2), pneumatoceles (4
), lung abscess
(1), mechanical ventilation >48 h (2), severe anemia requiring blood transfusion (2), severe hypoalbuminemia requiring seroalbumin replacement (1).

Serotype 3 compared withHIDP and LIDP groups combined.

...DESCRIPTORS: Bacterial pneumonia--...

...Bacterial pneumonia--...

...Pneumonia--...

...Pneumonia--

14/3,K/33 (Item 6 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

03532133 SUPPLIER NUMBER: 173420973 (USE FORMAT 7 OR 9 FOR FULL TEXT)
International Circumpolar Surveillance System for invasive pneumococcal disease, 1999-2005.(RESEARCH)
Bruce, Michael G.; Deeks, Shelley L.; Zulz, Tammy; Bruden, Dana; Navarro, Christine; Lovgren, Marguerite; Jette, Louise; Kristinsson, Karl; Sigmundsdottir, Gudrun; Jensen, Knud Brinklov; Lovoll, Oistein; Nuorti, J. Pekka; Herva, Elja; Nystedt, Anders; Sjostedt, Anders; Koch, Anders; Hennessy, Thomas W.; Parkinson, Alan J.
Emerging Infectious Diseases, 14, 1, 25(9)
Jan,
2008
PUBLICATION FORMAT: Magazine/Journal ISSN: 1080-6040 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Academic; Professional
WORD COUNT: 6215 LINE COUNT: 00730

TEXT:
...a population-based surveillance network for invasive bacterial disease in the Arctic. The 7-valent pneumococcal conjugate vaccine (PCV7) was introduced for routine infant vaccination in Alaska (2001), northern Canada (2002-2006), and Norway (2006). Data for invasive pneumococcal disease (IPD) were analyzed to identify clinical findings, disease rates, serotype distribution, and antimicrobial drug susceptibility; 11,244 IPD cases were reported. Pneumonia and bacteremia were common clinical findings. Rates of IPD among indigenous persons in Alaska and...
... Circumpolar Surveillance interlaboratory quality control programme, 1999-2004 (abstract). Clin Microbiol Infect. 2007;13(Suppl 1): 176.
(8.) Proulx JF, Dery S, Jette LP, Ismael J, Libman M, De Wals R Pneumonia epidemic caused by a virulent strain of Streptococcus pneumoniae serotype 1 in Nunavik, Quebec. Can Commun Dis Rep. 2002;28:129-31.
(9.) Macey JF, Roberts A, Lior L, Tam TW, VanCaeseele R Outbreak of community-acquired pneumonia in Nunavut, October and November, 2000. Can Commun Dis Rep. 2002;28:131-8.
(10...

...R, Danila R, Pilishvili T, Facklam R, Farley MM, et al. Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. JAMA. 2005;294:2043-51.
(12.) Schuchat A, Robinson K, Wenger JD, Harrison LH...

...337:970-6.
(13.) Dahl MS, Trollfors B, Claesson BA, Brandberg LL, Rosengren A. Invasive pneumococcal infections in Southwestern Sweden: a second follow-up period of 15 years. Scand J Infect Dis. 2001;33: 667-72.
(14.) Flannery B, Schrag S, Bennett NM, Lynfield R, Harrison LH, Reingold A, et al. Impact of childhood vaccination on racial disparities in invasive Streptococcus pneumoniae infections. JAMA. 2004;291:2197-203.
(15.) Hennessy TW, Singleton RJ, Bulkow LR, Bruden DL, Hurlburt DA, Parks D, et al. Impact of heptavalent pneumococcal conjugate vaccine on invasive disease, antimicrobial resistance and colonization in

Alaska Natives: progress towards elimination of...

...Levine OS, O'Brien KL, Knoll M, Adegbola RA, Black S, Cherian T, et al. Pneumococcal vaccination in developing countries. Lancet. 2006;367:1880-2.

(17.) Poehling KA, Talbot TR, Griffin MR, Craig AS, Whitney CG, Zell E, et al. Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. JAMA. 2006;295:1668-74.

(18.) Whitney CG. Impact of conjugate pneumococcal vaccines. Pediatr Infect Dis J. 2005;24:729-30.

(19.) Butler JC, Parkinson AJ, Funk...

...Singleton RJ, Hennessy TW, Bulkow LR, Hammitt LL, Zulz T, Hurlburt DA, et al. Invasive pneumococcal disease caused by nonvaccine serotypes among Alaska native children with high levels of 7-valent pneumococcal conjugate vaccine coverage. JAMA. 2007;297: 1784-92.

(21.) Koch A, Bruce M, Homoe P. Infectious...

...Roche PW, Krause VL, Bartlett M, Coleman D, Cook H, Davis C, et al. Invasive pneumococcal disease in Australia, 2004. Commun Dis Intell. 2006;30:80-92.

(23.) Cortese MM, Wolff M, Almeido-Hill J, Reid R, Ketcham J, Santosham M. High incidence rates of invasive pneumococcal disease in the White Mountain Apache population. Arch Intern Med. 1992; 152:2277-82.

(24 Streptococcus pneumoniae among Navajo children in the era before use of conjugate pneumococcal vaccines, 1989-1996. Am J Epidemiol. 2004; 160:270-8.

(25.) Voss L, Lennon D, Okesene-Gafa K, Ameratunga S, Martin D. Invasive pneumococcal disease in a pediatric population, Auckland, New Zealand. Pediatr Infect Dis J. 1994; 13:873...

...Fraser D, Givon-Lavi N, Bilenko N, Dagan R. Adecade (1989-1998) of pediatric invasive pneumococcal disease in 2 populations residing in 1 geographic location: implications for vaccine choice. Clin Infect Dis. 2001;33:421-7.

(27.) Whitney...
...Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med. 2003;348:1737-46.

(28.) Rudolph KM, Parkinson AJ, Reasonover AL, Bulkow LR, Parks D J, Butler JC. Serotype distribution and antimicrobial resistance patterns of invasive isolates of Streptococcus pneumoniae: Alaska, 1991-1998. J Infect Dis. 2000;182:490-6.

(29.) Karchmer AW. Increased antibiotic resistance in respiratory tract pathogens: PROTEKT US--an update. Clin Infect Dis. 2004;39(Suppl 3):S142-50.

(30.) Whitney CG, Farley MM, Hadler J, Harrison LH, Lexau C, Reingold A, et al. Increasing prevalence of multidrug-resistant Streptococcus pneumoniae in the United States. N Engl J Med. 2000;343: 1917-24.

Michael G. Bruce, * Shelley L. Deeks, ((dagger))(1) Tammy Zulz, * Dana Bruden, * Christine Navarro, ((dagger)) Marguerite Lovgren, ((double dagger)) Louise Jette, ((section)) Karl...

...Koch, (#)(#) Thomas W. Hennessy, * Alan J. Parkinson, * and the International Circumpolar Surveillance System for Invasive Pneumococcal Disease Working Group (2)

* Centers for Disease Control and Prevention, Anchorage, Alaska, USA; ((dagger)) Public...

...Hospital, Lulea, Sweden; ((paragraph))((paragraph))Umea University,

Umea, Sweden; and (#)(#) Statens Serum Institut, Copenhagen, Denmark
(1) Current affiliation: National Centre for Immunisation, Research and Surveillance, Westmead, New South Wales, Australia
(2) The International Circumpolar Surveillance System for Invasive Pneumococcal Disease Working Group: Jean-Francois Proulx (Department of Public Health, Nunavik Regional Board of Health...

...and Prevention, 4055 Tudor Centre Dr, Anchorage, AK 99508, USA; email: zwa8@cdc.gov

Table 1. Demographics of countries participating in the study

Characteristic	Alaska	Northern Canada	Greenland
Mean population	641,720	132,956	56,617
% Indigenous	19	59	Unknown
Region size, (km.sup.2)	1,518,807	4,506,600	2,131,863
No. participating laboratories	23	14	15
Location of reference laboratories	Anchorage	Edmonton, Montreal, Winnipeg	Nuuk, Copenhagen

Characteristic	Iceland	Norway	Northern Sweden	Finland
Mean population	288,035	4,565,943	252,729	5,215,791
% Indigenous	Unknown	<1	<5	<1
Region size, (km.sup.2)	102,968	323,760	160,580	339,290
No. participating laboratories	10	33	1	23
Location of reference laboratories	Reykjavik	Oslo, Tromso	Stockholm	Oulu

Table 2. Characteristics of persons with invasive pneumococcal disease, by country *

Characteristic	Alaska, 1999-2005, n = 769	Northern Canada, 1999-2005, n = 251	Greenland, 2000-2005, n = 69
Median age (range)	41.6 (1 mo-100 y)	30.2 (0 mo-83 y)	44.7 (0 mo-91 y)
No. males (%)	423 (55...		
...hospitalized (%)	585 (77)	201 (87) ((double dagger))	62 (100) ((double dagger))
Duration of hospitalization, d, median (minimum-maximum)	4 (0-188)	5 (0-77)	9 (0-131)
No. deaths (%)	96 (13) ((section))	11 (5) ((section))	13 (20) ((section))

Characteristic	Iceland, 2000-2005,	Norway, 2000-2005,

Characteristic	n = 274	n = 5,744
Median age (range)	53.2 (1 mo-98 y)	63.2 (0 mo-99 y)
No. males (%)	145 (53)	2,856 (99)
No. indigenous (%)	NA	NA
No. hospitalized (%)	NA	5,567 (99) ((double dagger))
Duration of hospitalization, d, median (minimum-maximum)	NA	NA
No. deaths...		

...section)) 419 (9) ((section))

Characteristic	Northern Sweden, 2003-2005, n = 88	Finland, 2000-2005, n = 4,049
Median age (range)	65.8 (9 mo-98 y)	54.2 (0 mo-100...

...21
(northern Canada), 7 (Greenland), and 127 (Norway) cases. Denominators are 760, 230, 62, and 5,617, respectively.

((section)) Death information missing for 10 (Alaska), 21 (northern Canada), 3 (Greenland), 161 (Iceland), and 1
,1016 (Norway) cases.
Denominators are 759, 230, 66, 113, and 4,728, respectively.

Table 3. Annualized crude and standardized incidence rates (per 100,000 persons) of IPD by countries not using 7-valent pneumococcal
conjugate vaccine *

Statistic or age group	Greenland (2000-2005)	Iceland (2000-2005)	Norway (2000-2005)
Total no. cases	69	274	5
,744
Age-specific annualized incidence rates (no. cases)			
<2y	77.4
(8)	89.8 (45)	50.0 (355)
2-19 y	4.8 (5
)	6.8 (32)	4.9 (312)
20-64 y	25.5 (53)	8.9 (90)
14.5 (2,352)	
(greater than or equal to) 65 y	16.6 (3)
(107)	53.1
66.7 (2,725)	
Crude annualized incidence (all ages)	20.3
15.9	21.0	
Annualized age standardized incidence ((dagger))	19.8
.6	14
16.2	

Statistic or age group	Northern Sweden (2003-2005)	Finland (2000-2005)
Total no. cases	88	4,049
Age-specific annualized incidence rates (no. cases)		
<2y	21.1 (3)	52.3 (367)
2-19 y	0.0 (0)	5.0 (346)
20-64 y	9.3 (41)	10.9 (2,057)
(greater than or equal to) 65 y	30.9 (44)	26.6 (1,279)
Crude annualized incidence (all ages)	11.6	12.9
Annualized age standardized incidence ((dagger))	9.1	11.6

* IPD, invasive pneumococcal disease,

((dagger)) Rates adjusted to 2000 World Health Organization world standard population estimates.

Table 4
. Rates/100,000 cases of IPD in Alaska and Northern Canada before and after introduction...

...512	NA		
All ages, y	20.6 (257)	15.8 (512)	0.0004
<2	173.5 (69)	79.2 (82)	<0.0001
2-19	10.7 (40)	6.6 (64)	0.02
20-64	13.7 (104)	14.1 (278)	0.82
(greater than or equal to) 65	57.9 (44)	44.5 (88)	0.17
Indigenous, all ages	56.0 (133)	38.1 (239)	0.0003
<2 y	440.6 (47)	177.5 (50)	<0.0001
Nonindigenous, all ages	12.3 (124)	10.4 (273)	0.13
<2 y	75.7 (22)	42.5 (32)	0.05
PCV 7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) ((dagger))			
All ages, y	9.6 (120)	3.4 (110)	<0.0001
<2	128.3 (51)	15.5 (16)	<0.0001
2-19	5.6 (21)	1.6 (16)	0.0003
20-64	4.1 (31)	2.8 (55)	0.09
(greater than or equal to) 65	22.4 (17)	11.6 (23)	0.05
Indigenous, all ages	24.9 (59)	4.9 (31)	<0.0001
<2y	318.7 (34)	21.3 (6)	<0.0001
Nonindigenous, all ages	6.0 (61)	3.0 (79)	<0.0001

<2y	58.5 (17)	13.3 (10)	<0.0001
Non-PCV7 serotypes ((dagger))			
All ages, y	8.3 (104)	10.5 (341)	0.04
-2	27.7 (11)	59.0 (61)	0.03
2-19	3.5 (13)	4.1 (40)	0.65
20-64	7.3 (55)	9.6 (189)	0.07
(greater than or equal to) 65	32.9 (25...	...187)	0.01
<2y	65.6 (7)	145.6 (41)	0.05
Nonindigenous, all ages	5.5 (56)	5.9 (154)	0.71
<2y	13.8 (4)	26.6 (20)	0.26
Penicillin nonsusceptible IPD, all serotypes ((double dagger))			
All ages	4.0 (50)	2.1 (68)	0.0004
<2y	62.9 (25)	21.3 (22)	<0.0001
Cotrimoxazole nonsusceptible IPD, all serotypes ((double dagger))			
All ages	5.6 (70)	3.0 (96)	0.0003
<2 y	90.5 (36)	25.1 (26)	<0.0001

Northern Canada

Group	Prevaccine (1999-2002)	Vaccine implementation (2003-2005)	p...
...23.8 (74)	18.8 (44)	0.24	
(greater than or equal to) 65	64.4 (14)	73.5(12)	0.84
Indigenous, all ages	44.2 (134)	25.0 (57)	0.0005
<2 y	229.3 (33)	92.6 (10)	0.01
Nonindigenous, all ages	9.6 (20)	10.2 (16)	0.86
<2 y	65.4 (3)	87.2 (3)	1.00
PCV 7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) ((dagger))			
All ages, y	12.6 (67)	3.8 (15)	<0.0001
<2	128.9 (25)	20.6 (3)	0.0008
2-19	8.4 (15)	1.5 (2)	0.01
20-64	7.1 (22)	1.7 (4)	0.005
(greater than or equal to) 65	23.0 (5)	36.8 (6)	0.55
Indigenous, all ages	17.1 (52)	3.5 (8)	<0.0001
<2y	159.8 (23)	9.3 (1	

) 0.0001
Nonindigenous, all ages 6.2 (13) 3.2 (5
) 0.24
<2y 43.6 (2) 29.1 (1
) 1.00
Non-PCV7 serotypes ((dagger))
All ages, y 17.1
(91) 16.8 (67) 0.94
-2 41.2 (8) 75.6 (11) 0.25
2-19 14.5 (26) 7.
4 (10) 0.09
20-64 15.4
(48) 16.7 (39) 0.75
(greater than or equal to) 65 41.4 (9) 36.8 (6)
1.00
Indigenous, all ages 25.4
(77) 20.2 (46) 0.24
<2y 48.6 (7) 74.1
(8) 0.44
Nonindigenous, all ages 2.9 (6) 7.0 (11) 0.09
<2y 21.8 (1) 58.1
(2) 0.58
Penicillin nonsusceptible IPD,
all serotypes ((double dagger))

All ages 1.5 (8) 0.8 (
3) 0.37
<2y 10.3
(2) 0.0 (0) 0.51
Cotrimoxazole nonsusceptible
IPD, all serotypes ((double
dagger))
All ages 2.6 (14) 1
.8 (7) 0.50
<2 y 15.5 (3
) 13.7 (2) 1.00

* IPD, invasive pneumococcal disease, PCV7, 7-valent
pneumococcal
conjugate
vaccine; NA, not available. Values in parentheses are no.
cases.

((dagger)) Serotype
available for 675 (88%) of 769 Alaska isolates and
240 (96%) of 251 Northern Canada...

...677
(88%) of 769 Alaska isolates and 236 (94%) of 251 northern Canada
isolates.

Table 5. Most prevalent serotypes in 6 countries reporting
Streptococcus pneumoniae type to ICS and proportion of isolates
covered by PCV7 and PCV13 vaccines *

	Alaska		Canada...	
...2000,	2001-2005,	1999-2002,	2003-2005,	
	n = 224	n = 453	n = 158	n = 82
1	14 (17%)	19A (11%)	1 (34%)	1 (24%)
2	4, 7F (9%)	4 (8%)		

14(11%) 8(11%)
3 9V (8%) 12F (8%) 4
(9%) 3 (7%)
4 19F (6%) 3, 7F
, 8 (7%) 8 (8%) 10A, 18C,
22F (6%)
5 6B (6%) 14 (6%) 6B
, 9V (6%) 6B (5%)

Proportion of serotyped isolates covered by PCV7 and PCV13 vaccines (<2 y of age)

PCV7	82% (51/62)	21% (16/77)	76% (25/33)	21% (3/14)
PCV13	92% (57/62)	57% (44/77)	94% (31/33)	43% (6/14)

Rank	Greenland, n = 60	Iceland, n = 269	Norway, n = 291	Finland, n = 3,947
1	1 (22%)	7 (20%)	4, 14 (18%)	14,4(12%)
2	12F (15%)	14 (12%)	9 (11%)	9V (8%)
3	4 (12%)	23 (12%)	6 (9%)	3, 23F, 7F (7%)
4	22F (8%)	19 (10%)	23 (8%)	6B (6%)
5	3 (7%)	9 (10%)	7 (7%)	19A, 19F (4%)

Proportion of serotyped isolates covered by PCV7 and PCV13 vaccines (<2 y of age)

PCV7	50% (3/6)	51% (23/45)	37% (10/27)	NA
PCV13	83% (5/6)	60% (27/45)	56% (15/27)	NA

* ICS, International Circumpolar Surveillance; PCV7, 7-valent pneumococcal conjugate vaccine (serotypes 4, 613, 9V, 14,18C, 19F, and 23F); PCV13, 13-valent pneumococcal conjugate vaccine (7 PCV7sero types plus 1, 3, 5, 6A, 7F, and 19A); NA, not available

Table 6. Proportion of isolates with nonsusceptibilitv to antimicrobial drugs in countries...

...62) 13 (10/77)
All ages 21 (47/223) 8 (37/452)
Ceftriaxone <2 23 (14/62) 5 (4/77)
((dagger)) All ages 11 (25/224) 1 (6/453)
Penicillin <2 40 (25/62) 29 (22/77)
(double dagger)) All ages 22...

...Age Pre-PCV7, Post-PCV7,
drug group, y % (n/N) % (n/N)

Cotrimoxazole	<2	9 (3/33)	17 (2/12)
	All ages	9 (14/158)	9 (7/78)
Erythromycin	<2	0 (0/33)	8 (1/13)
	All ages	1 (1/157)	5 (

4/79)

Ceftriaxone	<2	6 (2/33)	0 (0/12)
((dagger))	All ages	4 (7/159)	0 (0/80)
Penicillin	<2	6 (2/33)	0 (0/13)
(double dagger))	All ages	5 (8/159)	4 (3

/81)

Antimicrobial drug	Age group, y	Iceland, % (n/N)	Northern Sweden, % (n/N)
Cotrimoxazole	<2	35 (13/37)	100 (1/1)
	All ages	18 (43/234)	12 (3/25)
Erythromycin	<2	26 (10/38)	0 (0/2)
	All ages	9 (21/235)	6 (3/53)
Ceftriaxone	<2	0 (0/10)	NA
((dagger))	All ages	0 (0/39)	NA
Penicillin	<2	13 (5/38)	0 (0/1)
(double dagger))	All ages	8 (20/236)	2 (1/52)

* ICS, International Circumpolar Surveillance; PCV7, 7-valent pneumococcal conjugate vaccine; NA, not available.

((dagger)) Greenland reported nonsusceptibility of 0% (0/38) to ceftriaxone among...

...dagger)) Greenland reported nonsusceptibility of 0% (0/41) and Finland reported nonsusceptibility of 6% (236/4

,049) to penicillin among all ages. Finland reported nonsusceptibility of 9% (33/367) to penicillin among cases <2 y of age.

Table 7. Clinical findings for invasive pneumococcal disease

Findings	Alaska, 1999-2005, no. (%)	Northern Canada, 1999-2005, no. (%)
Pneumonia with bacteremia	466 (61)	162 (65)
Sepsis	154 (20)	41 (16)
Bacteremia	20 (3)	13 (5)
Meningitis with bacteremia	53 (7)	16 (6)
Other *	76 (10)	19 (8)
Total	769 (100)	251 (100)

Findings	Greenland, 2000-2005, no. (%)	Norway, 2000-2005, no. (%)
Pneumonia with bacteremia	36 (52)	2,598 (45)
Sepsis	14 (20)	1,404 (25)
Bacteremia	0	864 (15)
Meningitis with bacteremia	14 (20)	454 (8)
Other *	5 (7)	405 (7)
Total	69 (100)	5,725 (100)

* Empyema, cellulitis, necrotizing fasciitis, septic arthritis.

Table 8. Risk factors and medical conditions in persons (greater than or equal to) 18 years of age with invasive pneumococcal disease *

Factor or condition	Alaska, 1999-2005, no. (%)	Northern Canada, 1999-2005, no. (%)
Cigarette smoking...		
...201 (39)	50 (37)	
Chronic lung disease/asthma	139 (27)	26 (19)
Diabetes mellitus	71 (14)	22 (16)
Immunosuppressive therapy	35 (7)	5 (4)
Injection drug use	11 (2)	3 (2)
Asplenia	9 (2)	4 (3)
Total	509 (100)	135 (100)

* Risk factors and medical conditions are not mutually exclusive. Each case may have >1 condition reported. Data were not available for Greenland, Iceland, Norway, northern Sweden, or Finland.

((dagger...

...DESCRIPTORS: Pneumococcal infections...

...Pneumococcal infections

14/3,K/34 (Item 7 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

02915457 SUPPLIER NUMBER: 68155230 (USE FORMAT 7 OR 9 FOR FULL TEXT)
What you should know about the latest pneumococcal vaccine.
GAVIN, PATRICK J.; YOGEV, RAM; TAN, TINA Q.
Journal of Respiratory Diseases, 21, 11, 699
Nov,
2000
PUBLICATION FORMAT: Magazine/Journal ISSN: 0194-259X LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 6562 LINE COUNT: 00566

What you should know about the latest pneumococcal vaccine.

ABSTRACT: Streptococcus pneumoniae continues to be a common cause of pneumonia, bacteremia, acute otitis media (AOM), and sinusitis. This pathogen causes about 40,000 deaths annually in the United States. The 23-valent pneumococcal polysaccharide vaccine effectively prevents Spneumoniae infection in many patient populations) but it is not recommended...

...children younger than 2 years--a group that has a particularly high incidence of invasive pneumococcal disease. Recently, a heptavalent pneumococcal conjugate vaccine (PCV) was approved for infants and toddlers, beginning at 2 months of age. This vaccine contains the 7 serotypes that account for most cases of invasive pneumococcal disease and AOM in US children and has an efficacy rate of 97% against invasive...

...adverse effects. (J Respir Dis. 2000;21(11):699-707)

In the United States, Streptococcus pneumoniae is the leading cause of invasive bacterial infections and acute otitis media (AOM) in infants and young children. It is also a common cause of community-acquired pneumonia, bacteremia, and sinusitis. (1) S pneumoniae infections remain major causes of morbidity and mortality in the United States and especially in developing countries. (2-5) In the United States alone, S pneumoniae infection is responsible for 40,000 deaths annually, accounting for more deaths than any other vaccine-preventable disease. (5,6) The highest attack rates are in young children and the elderly (5,7)

Because of poor immunogenicity and unclear efficacy in infants and young children, the 23-valent pneumococcal polysaccharide vaccine is not recommended for routine immunization of children younger than 2 years, (2) which is the population with the highest attack rate for invasive and local pneumococcal diseases (the annual incidence of invasive pneumococcal disease is 160 cases per 100,000 population). (5) Also, the extent and severity of pneumococcal disease and the increasing spread of antibiotic-resistant S pneumoniae have made the development of an effective vaccine for infants and young children a global health priority.

Recently, the FDA approved a heptavalent pneumococcal conjugate vaccine (PCV) for universal immunization of infants and toddlers, beginning at 2 months of age, to prevent most invasive diseases caused by S pneumoniae. (1) In this article, we will focus on the epidemiologic and immunologic issues involved in the...

...the likely future implications of its widespread use.

MICROBIOLOGY

More than 90 serotypes of S pneumoniae, designated by number, have been identified based on antigenic differences in their capsular polysaccharides (Figure...

...related serotypes are distinguished from one another by letter--for example, serogroup 6 contains serotypes 6A and 6B. (9,10)

One of the reasons the Haemophilus influenzae type b (Hib) conjugate vaccines were so successful in virtually eradicating Hib disease in the developed world is that almost all H influenzae invasive diseases are caused by the b serotype. (11) The situation is more complex for S pneumoniae, because there are at least 40 potentially pathogenic serogroups. (12) Although all of the pathogenic...

...disease, with certain serogroups being more strongly associated with specific disease manifestations--for example, serogroups 1 and 14 are more often isolated from blood; serogroups 6, 10, and 23, from cerebrospinal fluid; and serogroups 3, 19, and 23, from middle-ear fluid. (9,10,12)

The most common serotypes causing disease differ among geographic areas; in the United States, 7 pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) are responsible for more than 80% of invasive disease and more than 60% of AOM among children. (12,13) In contrast, outside of North America and Europe, serogroups 1 and 5 are among the top 3 most frequent causes of invasive disease. (9)

EPIDEMIOLOGY

The spectrum of pneumococcal illness in infants and young children ranges from localized mucosal infections, such as AOM and sinusitis, to life-threatening invasive diseases, such as pneumonia and meningitis. In the United States, S pneumoniae accounts for 7 million cases of AOM, 500,000 cases of pneumonia, 50,000 cases of bacteremia, and 3000 cases of meningitis per year (Table). (5) Less commonly, S pneumoniae causes infections of bone and joints, infections of skin and soft tissues, endocarditis, parostitis, neonatal septicemia, primary peritonitis, and salpingitis.

S pneumoniae is the most common bacterial cause of AOM, accounting for up to 44% of cases. (14) It is estimated that 25% of pediatrician visits are for AOM and its sequelae, (15) translating into $2 billion in health care costs (by 1989 standards) per annum. (14) S pneumoniae is also the most common cause of bacterial meningitis in children in developed (16) and developing countries. (3) This pathogen accounts for 25% to 40% of the cases of bacterial meningitis in US ...

...and cephalosporin-nonsusceptible, which will probably increase morbidity and mortality further. (16)

In developing countries, pneumonia is a leading cause of death among children younger than 5 years, killing more than 4 million children every year. (2,9) S pneumomiae accounts for 20% to 25% of these deaths. In infants and young children, the clinical presentation of pneumococcal pneumonia is varied, ranging from mild, nonspecific respiratory symptoms to severe respiratory distress and lifethreatening disease. (20) In recent years, common complications associated with more severe pneumococcal disease, such as necrotizing pneumonia, empyema, and lung abscesses, appear to be increasing in incidence.(21)

PATHOGENESIS AND VIRULENCE

Pneumococcal virulence is determined by the capsular polysaccharide, which protects the organism from phagocytosis and complement-mediated lysis. (22-24) Opsonization by serotype-specific antibodies against capsular polysaccharide antigens is the primary host defense against S pneumoniae. (23,25) Therefore, resolution of pneumococcal disease begins only after the appearance of anticapsular antibodies, which facilitate polymorphonuclear phagocytosis and complement-mediated lysis of the pneumococci. (23,24)

Nasopharyngeal colonization is a prerequisite for invasive disease, with the transition from asymptomatic...

...most often after acquisition of a new strain; 15% of children who acquire a new pneumococcal serotype become ill (usually with AOM) within 1 month. (28) Unfortunately, the serogroups of S penumoniae, which are most commonly associated with antibiotic...

...antibiotic pressure.

ANTIBIOTIC RESISTANCE

Over the last several decades, the incidence of antibiotic-resistant S pneumoniae has continued to grow worldwide. (31) A recent 3 -year multicenter study of systemic pneumococcal infections in US children (two thirds of whom were younger than 2 years) demonstrated an...

...nonsusceptible to penicillin and ceftriaxone, respectively. More than 90% of the resistant strains belonged to 5 serotypes (6, 9, 14, 19, and 23). (32) Recent data from a 1997 US surveillance study demonstrated that 51% of pneumococcal isolates were pencillin-nonsusceptible, and an increase in the degree of resistance was noted. (33)

This increase in resistance, followed by reports of treatment failures, has made the treatment of pneumococcal disease, especially meningitis, more difficult. (34) Thus, new guidelines for empiric treatment of suspected pneumococcal meningitis, AOM, and adult community-acquired pneumonia were recently developed. (35) Antibiotic-resistant strains of S pneumoniae are carried more often by infants and young children than by adults. (36,37) The exchange and recombination of capsular serotypes that occur commonly within natural populations of S pneumoniae is 1 mechanism that enhances the spread of a multiantibiotic-resistant phenotype to previously sensitive serotypes. (37...

...and transmit it to household members. (32,36)

Eradication of nasopharyngeal carriage of resistant S pneumoniae in the day-care population is difficult, (36,37) but an effective vaccine may reduce carriage rates, especially in day-care attendees, and thereby limit the spread of resistant pneumococci in the community.

IMMUNITY AGAINST S PNEUMONIAE

Natural immunity

The presence of serotype-specific antibody against pneumococcal capsular polysaccharide is thought to confer protective immunity against pneumococcal disease. (39-41) However, the ability to produce an antibody response to the capsular polysaccharide antigens of encapsulated bacteria, such as S pneumoniae, Hib, and Neisseria meningitidis, is generally poor or absent during the first 2 years of...

...presence of a late developing subset of mature B lymphocytes, which carry the costimulatory CD2 1 complement receptor. The immature B lymphocytes of infants and young children have reduced levels of...

...respond to polysaccharide antigens leads to a failure to produce protective antibodies in response to pneumococcal infection or polysaccharide vaccine, leaving infants and young children susceptible to pneumococcal infection. (39,42)

Vaccine immunity

The 23-valent pneumococcal polysaccharide vaccine, licensed in the United States since 1983, contains the purified pneumococcal polysaccharide capsular antigens of the 23 most common disease-causing serotypes. (22) It has proven efficacy in preventing invasive pneumococcal infections in immunocompetent adults (44); however, very few of the serotypes contained in the vaccine are sufficiently immunogenic in children younger than 2 years. Unfortunately, the pneumococcal serotypes that most commonly cause disease (6A, 14, 19F, and 23F) demonstrate the poorest immunogenicity in children. (7,44-47) Thus, the polysaccharide vaccine is not...

...immunologic memory and to prime for an anamnestic response, the polysaccharide vaccine does not reduce pneumococcal mucosal carriage. Thus, it does not provide any significant protection against mucosal disease, such as AOM and sinusitis, or against the spread of antibiotic-resistant pneumococci in infants and young children. (7,40,41,46) The protective efficacy of the pneumococcal polysaccharide vaccine is also generally poor among immunocompromised patients and the elderly, with a lack...

...PCV

To solve the problem of decreased immunogenicity associated with the polysaccharide vaccine in infants, conjugate vaccines have been developed, coupling the epidemiologically most important pneumococcal serotypes to various protein carriers. This technology is similar to the one used for the Hib conjugate vaccine. Carrier proteins tested during development of the PCV include diphtheria and tetanus toxoids, the mutant diphtheria toxin CRM197, and meningococcal outer membrane protein complex. (40)

While the Hib conjugate vaccine coupled a polysaccharide of 1 serotype to a protein carrier, the serotypic diversity of the pneumococcal capsule presents major challenges to the design of the PCV. Compared with the previous 23valent pneumococcal polysaccharide vaccine, conjugation to a protein carrier limits the number of serotypes that can be included in the PCV. Thus, potential PCV efficacy relies on knowledge of the epidemiology of pneumococcal serotypes causing disease in different populations and geographic regions. (9,12)

As noted above, 7 pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) account for more than 80% of invasive disease and more than 60% of AOM cases...

...These serotypes were chosen to be included in the currently licensed heptavalent PCV. In addition, 5 of these serotypes (6B, 9V, 14, 19F, and 23F) are most frequently associated with antibiotic-resistant S pneumoniae infections in the United States. (34)

The addition of serotypes 1 and 5, which are common causes of invasive disease in developing countries, produces the nonavalent conjugate vaccine, and the further addition of serotypes 3 and 7F makes up the 11-valent conjugate vaccine, both of which are currently being evaluated in clinical trials. The addition of these serotypes increases the coverage of the PCV to 90% of the pneumococcal serotypes that cause invasive disease in US children. The nonavalent PCV, which contains the 7 most common pneumococcal serotypes that cause invasive disease in Latin America and 6 of the 7 in Africa and Asia, has the potential to prevent most invasive pneumococcal diseases in developing countries. (12)

Safety

In clinical trials that have been performed since 1992...

...childhood immunizations. (40,45,50,52)

When the PCV booster was given concurrently with Hib conjugate vaccine and diphtheria and tetanus toxoids and acellular pertussis (DTaP) vaccine, no interference was demonstrated...
...were uniformly very high. Any observed decrease in antibody responses to DTaP vaccine and Hib conjugate vaccine was considered to be clinically nonsignificant. (50,53) Thus, the PCV was subsequently incorporated...

...preexisting childhood immunization schedule. (54)

Immunogenicity

In multiple studies, the primary series of 2 or 3 doses of the PCV has demonstrated good immunogenicity, as defined by at least a 2-fold increase in antibody concentration against the vaccine serotypes (including serotypes 6B and 23F, which are poorly immunogenic when given in the polysaccharide vaccine). These studies have demonstrated that...

...children and in children with sickle cell anemia (who are at increased risk for invasive pneumococcal disease (1,57)) show that the PCV is safe and more immunogenic than the 23-valent polysaccharide...

...58-60) It is hoped that other groups of children at high risk for invasive pneumococcal disease who are not protected by the current polysaccharide vaccine will also benefit from the increased antibody response to the PCV. (22,32)

Although the highest attack rates for pneumococcal disease are seen in infants and young children, most deaths from pneumococcal disease in developed countries occur in the elderly. (2) Given that the current pneumococcal polysaccharide vaccine is only 40% effective in preventing invasive pneumococcal disease in immunocompetent elderly patients, (44) the demonstrated ability of the PCV to prime for...

...very likely to produce enhanced protection for the elderly. (61) Thus, the new PCV is 1 of the few vaccines with the potential for substantial public health benefit in adults as...

...infants in northern California who randomly received either heptavalent PCV or an investigational meningococcal C conjugate vaccine at 2, 4, 6, and 12 to 15 months of age, PCV demonstrated an efficacy rate of 97% (95% confidence interval, 82.7% to 99.9%) against invasive pneumococcal disease caused by the 7 vaccine serotypes. When invasive disease caused by nonvaccine serotypes was...

...89% efficacy rate. (55) The PCV had an efficacy rate of 11% to 63%

against pneumonia, depending on the diagnostic criteria used (physical examination findings alone vs definite consolidation on chest radiograph, respectively). (55)

Prevention of mucosal carriage and disease

The ability of the Hib conjugate vaccine to reduce nasopharyngeal carriage and decrease transmission to healthy children has produced a herd...

...65) Several studies have documented the PCV'S ability to reduce carriage of vaccine-type pneumococci (including antibiotic-resistant strains) in infants and children vaccinated as early as 6 weeks to...

...eradication of the carrier state, suggesting that the PCV prevents or delays acquisition of new pneumococcal serotypes rather than eliminating established carriage. (66) The PCV appears to eradicate the carrier state...

...a 6% reduction in AOM episodes). (7) Of interest, a 34% reduction in episodes of pneumococcal AOM (irrespective of serotype) was noted in vaccine recipients. A study of nonavalent PCV in Israeli day-care attendees...

...vaccine recipients. (72)

Unlike Hib disease, which has almost disappeared following introduction of the Hib conjugate vaccine, widespread use of the PCV will result in reduction but not disappearance of pneumococcal disease, because of the diversity of invasive pneumococcal serotypes. Evidence from studies addressing whether selective PCV pressure will result in replacement of vaccine...

...nonvaccine serotypes following immunization with the PCV. (68)

Effect on antibiotic resistance

Increased use of pneumococcal vaccines, improved surveillance for the development of drug resistance, and promotion of judicious use of antibiotics form the basis of strategies to minimize the impact of drug-resistant pneumococci. (73) Antibiotic-resistant pneumococci belong to a limited number of serotypes, which are also the most common causes of...

...more prominent causes of disease in a population no longer protected by the PCV.

* S pneumoniae appears capable of transmitting capsular serotype and antibiotic resistance genetic determinants between different pneumococcal strains and between related streptococci. (38) Theoretically, the selective pressure of PCV and the transformational...

...nonvaccine serotypes. (38, 74) This would be of some concern for the future, although nonvaccine pneumococcal serotypes are usually of lower virulence than are serotypes covered by the vaccine. (74)

Potential impact on antibiotic use

Following extensive use of the PCV, it is predicted that invasive pneumococcal disease in children will decrease significantly. Based on observed efficacy against invasive pneumococcal disease (more than 95%), the PCV could prevent over 48,000 cases of bacteremia and...

...States yearly An efficacy of up to 9% against ACM and 11% to 63% against pneumonia may prevent 600,000 cases of ACM and 55,000 to 315,000 cases of pneumonia in the United States yearly.

In addition, limited data suggest that the PCV will decrease...

...Because the PCV protects only against a limited number of serotypes contained in the vaccine, 1 question that remains is: Would any future change in the pneumococcal serotypes causing disease result in

a resurgence of invasive disease in susceptible populations? Although the proportion of infections caused by various pneumococcal serotypes does change over time, only modest changes in serotype distribution have been demonstrated in the past. (13) It is postulated that following widespread PCV...

...current PCV is also likely to remain problematic for both developing and industrialized countries. S pneumoniae serotype 2, which is not included in any PCV, is responsible for up to 26% of invasive disease isolates in infants from developing countries. (4,12) It is estimated that nonvaccine serotypes (mostly 6A and 19A) account for 8% to 15% of invasive pneumococcal disease in young children in the United States. (12)

A single study from Gambia failed to demonstrate reduction in carriage of the nonvaccine serotype 6A by a PCV that contained the related 6B serotype. (66) It remains to be seen whether vaccine conjugates 6B, 9V, and 19F will provide cross-protection against disease caused by the related nonvaccine serotypes 6A, 9A, 9L or 9N, and 19A.

In the northern California vaccine study, all 7 PCV failures (in 6 infants with draining ears and 1 infant with bacteremic pneumonia) were caused by S pneumoniae serotype 19F. (55) This may be because certain pneumococcal serotypes either possess previously unrecognized virulence factors, as has been suggested by studies in children...

...model, or require higher antibody titers for protection. (75, 76)

The potential for shifts in serotype distribution over time, the issue of cross-protection for nonvaccine strains, and the potential requirement...

...infants and young children, inducing protective immune responses and preventing more than 95% of invasive pneumococcal diseases caused by vaccine serotypes. In addition, the PCV has the potential to prevent mucosal pneumococcal disease, decrease pneumococcal nasopharyngeal carriage, and by reducing antibiotic use remove the selective pressure driving the spread of antibiotic-resistant S pneumoniae. By greatly reducing the burden of pneumococcal disease and limiting the spread of antibiotic-resistant traits worldwide, the PCV represents another milestone...

...of healthy infants with PCVs is potentially cost-effective. Such immunization is projected to reduce pneumococcal disease costs by almost $760 million for each cohort of infants born in the United...

...of pediatrics, codirector pediatric travel medicine clinic, and attending physician, division of infectious diseases.

REFERENCES

(1.) American Academy of Pediatrics. Pneumococcal infections. In: Pickering LK, ed. 2000 Red Book: Report of the Committee of Infectious Diseases. 25th ed. Elk Grove Village, III: American Academy of Pediatrics; 2000.

(2.) World Health Organization. Pneumococcal vaccines. WHO position paper. Weekly Epidemiological Record. 1999;74:177-183.

(3.) The WHO Young Infant Study Group. Bacterial etiology of serious infections in young infants in...

...countries: results of a multicenter study. Pediatr Infect Dis J. 1999; 18 (suppl):S17-322.

(4.) World Health Organization. Vaccine research and development: report of the technical review group meeting, June 9-10, 1997. Geneva: World Health Organization; 1997:32-36.

(5.) Centers for Disease Control and Prevention. Prevention of

pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices. MMWR. 1997;46:1-24.
(6.) Gardner P. Schaffner W. Immunization of adults. N Engl J Med. 1993;328:1252-1258.
(7.) Klein JO. The pneumococcal conjugate vaccine arrives: a big win for kids. Pediatr Infect Dis J. 2000;19:181-182.
(8.) Scott JAG, Hall AJ, Dagan R, et al. Sero-group-specific epidemiology of Streptococcus pneumoniae: association with age, sex, geography in 7000 episodes of invasive disease. Clin Infect Dis. 1996:22:973-981.
(9.) Hausdorff WP, Bryant 1, Kloek C, et al. The contribution of specific pneumococcal serogroups to different disease manifestations: implications for conjugate vaccine formulation and use. Clin Infect Dis. 2000;30:122-140.
(10.) Schiffman G. Chemistry and immunochemistry of the pneumococcal polysaccharide vaccine with special reference to cross-reactions and immunological factors. Rev Infect Dis. 1981;3 (suppl):S18-S26.
(11.) Centers for Disease Control and Prevention. Impact of vaccines universally recommended...

...MMWR. 1999;48:243-248.
(12.) Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use. Clin Infect Dis. 2000;30:100-121.
(13.) Butler JC, Breiman RF, Lipman HB, et al. Serotype distribution of Streptococcus pneumoniae infections among preschool children in the United States, 1978-1994: implications for development of a conjugate vaccine. J Infect Dis. 1995;171:185-189.
(14.) Bluestone CD, Stephenson JS, Martin LM. Ten-year review of otitis media pathogens. Pediatr Infect Dis J. 1992;11(suppl):S7-S11.
(15.) Olson LC, Jackson MA. Only the pneumococcus. Pediatr Infect Dis J. 1999;18:849-850.
(16.) Schuchat A, Robinson K, Wenger JD...

...Dis J. 1993;12:389-394.
(18.) Kornlisse R, Westerbeek C, Spoor A, et al. Pneumococcal meningitis in children: prognostic indicators and outcome. Clin Infect Dis. 1995;21:1390-1397.
(19...

...Tan TQ, Mason EO, Barson WJ, et al. Clinical characteristics and outcome 01 children with pneumonia attributable to penicillin-susceptible and penicillin-nonsusceptible Streptococcus pneumoniae. Pediatrics. 1998;102:1369-1375.
(21.) Hardie W, Bukolic R, Garcia VF, et al. Pneumococcal pleural empyemas in children. Clin Infect Dis. 1996;22:1057-1063.
(22.) Peter G, Klein JO. Pneumococcal vaccine. Pediatr Rev. 1996;17:335-341.
(23.) Tuomanen El, Austrian R, Masure HR. Pathogenesis of pneumococcal infection. N Engl J Med. 1995;332:1280-1284.
(24.) Austrian R. Some observations on the pneumococcus and on the current status of pneumococcal disease prevention. Rev Infect Dis. 1981;3(suppl):S1-S17.
(25.) Vidarsson G, Jonsdottir I, Jonsson S, Valdimarsson H. Opsonization and antibodies to capsular and cell wall polysaccharides of Streptococcus pneumoniae. J Infect Dis. 1994;170:592-599.
(26.) Austrian R. Some aspects of the pneumococcal carrier state. J Antimicrob Chemother. ...35-45.
(27.) Ghaffar F, Friedland IR, McCracken GH. Dynamics of nasopharyngeal colonization by Streptococcus pneumoniae. Pediatr Infect Dis J. 1999;18:638-646.

(28.) Gray BM, Converse GM, Dillon HC. Epidemiologic studies of Streptococcus pneumoniae in infants: acquisition, carriage, and infection during the first 24 months of life. J Infect Dis. 1980;142:923-933.
(29.) Zenni MK, Cheatham SH, Thompson JM, et al. Streptococcus pneumoniae colonization in the young child: association with otitis media and resistance to penicillin. J Pediatr. 1995;127:533-537.
(30.) Hodges RG, McLeod CA, Bernhard WG. Epidemic pneumococcal pneumonia. III. Pneumococcal carrier studies. Am J Hyg. 1946;44:207-230.
(31.) Klugman KP. Pneumococcal resistance to antibiotics. Clin Microbiol Rev. 1990;3:171-196.
(32.) Kaplan SL, Mason EO, Barson WJ, et al. Three-year multicenter surveillance of systemic pneumococcal infections in children. Pediatrics. 1998;102:538-545.
(33.) Doern GV, Pfaller MA, Kugler K, et al. Prevalence of antimicrobial resistance among respiratory tract isolates of Streptococcus pneumoniae in North America: 1997 results from the SENTRY antimicrobial surveillance program. Clin Infect Dis. 1998...

...Butler JC, Hoffmann J, Cetron MS, et al. The continued emergence of drug resistant Streptococcus pneumoniae in the United States: an update from the Centers for Disease Control and Prevention's pneumococcal sentinel surveillance system. J Infect Dis. 1996;174:986-993.
(35.) Quagliarello VJ, Scheld WM...

...708-716.
(36.) Cherian T, Steinhoff MC, Harrison LH, et al. A cluster of invasive pneumococcal disease in young children in child care. JAMA. 1994;271:695-697.
(37.) Reichler MR, Allphin AA, Breiman RF, et al. The spread of multiply resistant Streptococcus pneumoniae at a day care center in Ohio. J Infect Dis. 1992;166:1346-1353.
(38.) Barnes DM, Whittier S, Gilligan P, et al. Transmission of multidrug-resistant serotype 23F Streptococcus pneumoniae in group day care: evidence suggesting capsular transformation of the resistant strain in vivo. J Infect Dis. 1995;171:890-896.
(39.) Siber GR. Pneumococcal disease: Prospects for a new generation of vaccines. Science. 1994;265:1385-1387.
(40.) Eskola J, Anttila M. Pneumococcal conjugate vaccine. Pediatr Infect Dis J. 1999;18:543-551.
(41.) Rubin LG. Pneumococcal vaccine. Pediatr Clin North Am. 2000;47:269-285.
(42.) Rijkers GT, Sanders EAM, Breukels...

...Thymus-independent and thymus-dependent responses to polysaccharide antigens. J Infect Dis. 1992;165(suppl 1):S49-S52.
(44.) Shapiro ED, Berg AT, Austrian R et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. N Engl J Med. 1991;325:1453-1460.
(45.) Kayhty H, Ahman H, Ronnberg P-R, et al. Pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine is immunogenic in infants and children. J Infect Dis. 1995;172:1273-1278.
(46.) Douglas RM, Paton JC, Duncan SJ, Hansman DJ. Antibody response to pneumococcal vaccination in children younger than five years of age. J Infect Dis. 1983;148:131-137.
(47.) Leinonen M, Sakkinen A, Kalliokoski R, et al. Antibody responses to 14-valent pneumococcal capsular polysaccharide vaccine in pre-school age children. Pediatr Infect Dis J. 1986;5 :39-44.
(48.) Butler JC, Breiman RF, Campbell JF, et al. Pneumococcal polysaccharide vaccine efficacy. JAMA. 1993;270:1826-1831.

(49.) Donaldson SS, Vosti KL, Berberich FR, et al. Response to pneumococcal vaccine among children with Hodgkin's disease. Rev Infect Dis. 1981;3(suppl):S133-S143.
(50.) Shinefield HR, Black S, Ray P, et al. Safety and immunogenicity of the heptavalent pneumococcal CRM 197 conjugate vaccine in intents and toddlers. Pediatr Infect Dis J. 1999;18:757-763.
(51.) Rennels MB, Edwards KM, Keyserling HL, et al. Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM 197 in United States infants. Pediatrics. 1998;101:604-611.
(52.) Ahman H, Kayhty H, Tamminen P. et al. Pentavalent pneumococcal oligosaccharide conjugate vaccine PncCRM is well-tolerated and able to induce an antibody response in infants. Pediatr ...

...15:134-139.
(53.) Daum RS, Hogerman D, Rennels MB, et al. Infant immunization with pneumococcal CRM197 vaccines: effect of saccharide size on immunogenicity and interactions with simultaneously administered vaccines. Pediatr...

...455.
(54.) American Academy of Pediatrics. Committee on Infectious Diseases. Recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. Pediatrics 2000;106:362-366.
(55.) Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis. J. 2000;19:187-195.
(56.) Vidarsson G, Sigurdardottir ST, Gudnason T, et al. Isotypes and opsonophagocytosis of pneumococcus type 6B antibodies elicited in infants and adults by an experimental pneumococcus type 6B -tetanus toxoid vaccine. Infect Immun. 1998;66:2866-2870.
(57.) Farley JJ, King JC, Nair P, et al. Invasive pneumococcal disease among infected and uninfected children of mothers with human immunodeficiency virus infection. J Pediatr...

...King JC, Vink PB, Farley JJ, et al. Safety and immungenicity of a five-valent pneumococcal conjugate vaccine in children younger than two years with and without human inmunodeficiency virus infection. Pediatrics. 1997;99:575-580.
(59.) Sarnaik S, Kaplan J, Schiffman G, et al. Studies on pneumococcus vaccine alone or mixed with DTP and on pneumococcus type 6B and Haemophilus influenzae type b capsular polysaccharide-tetanus toxoid conjugates in two to five year old children with sickle cell anemia. Pediatr Infect Dis J...

...JC, Vink PE, Farley JJ, et al. Comparison of the safety and immunogenicity of a pneumococcal conjugate with a licensed polysaccharide vaccine in human immunodeficiency virus and non-human immunodeficiency virus-infected...

...Dis J. 1996;15:192-196.
(61.) Chan CY, Molrine DC, George S, et al. Pneumoccooal conjugate vaccine primes for antibody responses to polysaccharide pneumococcal vaccine after treatment if Hodgkins disease. J Infect Dis. 1996;173:256-258
(62.) Takala...

...Santosham M, Almeido-Hill J, et el. Vaccination with Haemophilus influenzae type b meningococcal protein conjugate vaccine reduces oropharyngeal carriage of Haemophilus influenzae type b among American Indian children. Pediatr Infect...

...of oropharyngeal carriage of Haemophllus influenzae type b (Hib) in children immunized with an Hib conjugate vaccine. Pediatr Infect Dis J. 1991;164:982-986.

(64.) Murphy TV, Pastor P, Medley F, et al. Decreased Haemophilus colonization in children vaccinated with Haemophilus influenzae type b conjugate vaccine. J Pediatr. 1993;122:517-523.

(65.) Barbour ML, Mayon-White RT, Coles C, et al. The impact of conjugate vaccine on carriage of Haemophilus influenzae type b. J Infect Dis. 1995;171:93-98...

...Huebner RE, Waas AD, et al. Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. J Infect Dis. 1999;180:1171-1176.

(67.) Dagan R, Muallem M, Melamed R, et al. Reduction of pneumococcal nasopharyngeal carriage in early infancy after immunization with tetravalent pneumococcal vaccines conjugated to either tetanus toxoid or diphtheria toxoid. Pediatr Infect Dis J. 1997:16:1060-1064.

(68.) Dagan R, Melamed R, Muallem M, et al. Reduction of nasopharyngeal carriage of pneumococci during the second year of life by a heptavalent conjugate pneumococcal vaccine. Pediatr Infect Dis J. 1996:174:1271-1278.

(69.) Obaro Sk, Adegbola RA, Banya WAS, Greenwood BM. Carriage of pneumococci after pneumococcal vaccination. Lencet. 1996;348:271-272.

(70.) Nieminen T, Kathty H, Leroy O, Eskola J. Pneumococcal conjugate vaccine in toddlers: mucosal antibody response measured as circulating antibody-secreting cells and as salivary...

...J, Kilpi T, and the Finnish Otitis Media (FinOM) Study Group. Efficacy of a heptavalent pneumococcal conjugate vaccine (PncCRM) against serotype-specific, culture-confirmed pneumococcal acute otitis media (AOM) in infants and children. In: Program and abstracts of the 38th...

...9.

(72.) Dagan R, Sikuler-Cohen M, Givon-Lavi N, et al. A 9-valent pneumococcal CRM 197 vaccine has a major impact on morbidity and antibiotic use in day-care...
...1530.

(73.) Jerrigan DB, Cetron MS, Breiman RF. Minimizing the impact of drug-resistant Streptococcus pneumoniee. JAMA. 1996;275:206-209.

(74.) Coffey TJ, Enright MC, Daniels M, et al. Recombinant changes at the capsular biosynthetic locus lead to frequent serotype changes among natural isolates of Streptococcus pneumoniae. Molec Microbiol. 1998;27:73-83.

(75.) Briles DE, Crain MJ, Gray BM, et el. Strong association between capsular type and virulence for mice among human isolates of Streptococcus pneumoniae. Infect Immun. 1992;60:111-115.

(76.) Eskola J, Takala AK, Kela E, et al. Epidemiology of invasive pneumococcal infections in children in Finland. JAMA. 1992;268:3323-3327.

(77.) Lieu TE, Ray GT, Black SB, et al. Projected cost-effectiveness of pneumococcal conjugate vaccination of healthy infants and young children. JAMA. 2000;283:1460-1468.

14/3,K/35 (Item 8 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

01872143 SUPPLIER NUMBER: 57949372 (USE FORMAT 7 OR 9 FOR FULL TEXT)

Conjugate Pneumococcal Vaccine May Shift Otitis Etiology.
TUCKER, MIRIAM E.
Family Practice News, 29, 21, 32
Nov 1,
1999
PUBLICATION FORMAT: Tabloid ISSN: 0300-7073 LANGUAGE: English
RECORD TYPE: Fulltext TARGET AUDIENCE: Professional
WORD COUNT: 561 LINE COUNT: 00049

Conjugate Pneumococcal Vaccine May Shift Otitis Etiology.

TEXT:

...very likely be a shift in the bacterial causes of acute otitis media once the conjugate pneumococcal vaccine becomes firmly entrenched in the routine childhood immunization schedule, although it's not clear...

The heptavalent conjugate pneumococcal vaccine, manufactured by Wyeth-Lederle Vaccines, contains the seven strains of Streptococcus pneumoniae that most commonly infect children in the United States. Most of the resistant pneumococcal strains are also among those seven.

But two recent trials have shown that the vaccine...

...the conference, Dr. Block of Kentucky Pediatric Research Inc., Bardstown, offered evidence that nonvaccine S. pneumoniae serotypes and (beta)-lactamase-producing Haemophilus influenzae have already become more prevalent in AOM.

Among 413 pneumococcal isolates from children of all ages with AOM between 1992 and 1998, 57% were strains covered in the conjugate pneumococcal vaccine: 16% were serotype 19F; 10%, serotype 6B; 10%, serotype 23F; 8%, serotype 14; 8%, serotype 9V; 4%, serotype 18C; and 1%, serotype 4. This is the largest current series of serotyped pneumococcal isolates from an ambulatory population in the United States.

Three nonvaccine strains were more prevalent than some of the vaccine serotypes: 14% were serotype 3, 5% were serotype 6A, and 3% were serotype 19A. Serotype 19F accounted for 26% of penicillin-nonsusceptible strains, and 6A, for 12%.

It's not known whether there is crossprotection between strains 19A and 19F or 6A and 6B, Dr. Block noted.

Serotypes 1, 3, and 4 were much less common among children under 24 months of age, the key target for...

...think about adding serotypes that are more common and resistant in younger children, such as 6A and 19A. We're already seeing a significant shift. Close surveillance is going to be essential," Dr. Block said.

Wyeth-Lederle is doing preclinical testing of an 11-valent conjugate pneumococcal vaccine that includes the 7 in the heptavalent vaccine plus serotypes 1, 3, 5, and 7F.

Dr. Block and his associates also compared 279 middle ear isolates from children with AOM...

...Isolates were obtained by tympanocentesis or from spontaneously draining ears.

With universal use of the conjugate pneumococcal vaccine, "(beta)-lactamase-producing H. influenzae will become a major player in refractory AOM," Dr. Block speculated.

Among the S. pneumoniae isolates, those with intermediate resistance nearly doubled from 14% to 27%, while highly resistant strains fell from 15% to 10%. Overall, penicillin-nonsusceptible strains...

DESCRIPTORS: Pneumococcal vaccine...

14/3,K/36 (Item 9 from file: 149)
DIALOG(R)File 149:TGG Health&Wellness DB(SM)

01253908 SUPPLIER NUMBER: 08959393 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Pneumococcus and influenza. (editorial)
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The Lancet, v335, n8694, p898(4)
April 14,
1990
DOCUMENT TYPE: editorial PUBLICATION FORMAT: Magazine/Journal ISSN: 0099-5355 LANGUAGE: English RECORD TYPE: Fulltext; Abstract
TARGET AUDIENCE: Professional
WORD COUNT: 3025 LINE COUNT: 00294

Pneumococcus and influenza. (editorial)

ABSTRACT: A large number of people suffer, and many die, from infection with Streptococcus pneumoniae and influenza virus. Most infections with pneumococci (pneumonia and other illnesses) are due to a relatively few types of organism. This bacterium can...

...many people, then vanishes, to be replaced by a different influenza virus a year later. Pneumococcal infection, which kills up to 40,000 people per year in the United States, cannot...
...itself; and young children cannot make antibodies against the substance in the capsule. The current pneumococcus vaccine contains capsule fragments from 23 different varieties, and its effectiveness in high-risk groups...

...infection, show promise, and these are reviewed. In general, cold-adapted live influenza vaccine and conjugate polysaccharide-protein pneumococcus vaccine are the best hopes for fighting these two diseases. This is especially true in...

TEXT:

Pneumococcus and influenza By different mechanisms Streptococcus pneumoniae and influenza virus make a large contribution to morbidity and mortality from respiratory tract infection in man. Although pneumococci come in many serotypes, the antigenic structure of each capsular polysaccharide is stable, and most...

...just a few serotypes; the nasopharynx is often colonised without symptomatic infection, and a given serotype rarely causes invasive disease on more than one occasion. Influenza virus, on the other hand...

Pneumococcus

In the United States pneumococci cause 10-25% of all pneumonias with an estimated 40 000 deaths per year, bacteraemia in 15-19/100 000 persons per year, and meningitis in 1-2/100 000 persons per year. [1] By 3 years of age, over 20% of children have had one or more episodes of pneumococcal otitis media. Morbidity and mortality are even higher in developing countries; for example, pneumococcal pneumonia causes over 1 million deaths each year in children under 5 years old, and the US Institute of Medicine's 1985 review of new vaccines for developing countries gave the highest priority to development of a pneumococcal vaccine effective in infants. [2]

Antibiotic therapy alone will not be a satisfactory way to control

pneumococcal infection. First, antibiotic therapy does not reduce mortality in the first three days of treatment...

...proportion of the deaths occur; and, third, antibiotic resistance is likely to be increasingly troublesome. [3]

Why does S pneumoniae cause so much illness? The organism is a gram-positive bacterium with a polysaccharide capsule...

...immunity, and young children make little or no antibody to such T-cell-independent antigens. [4] In general, the serotypes that are highly pathogenic in infants (types 1, 2, 5, 6, 14, 18, 19, and 23) are those that give the weakest antibody response in this age group. [4]

Pneumococcal capsular polysaccharide vaccine

The first pneumococcus vaccine was produced in 1911, but not until 1945 was there unequivocal proof of its...

...current vaccine contains 25 [mu]g of polysaccharide from each of 23 serotypes (Danish types 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F). In the United States, vaccination is recommended for a wide range of conditions (see table). [1] These recommendations are controversial.

INDICATIONS FOR VACCINATION

Pneumococcal polysacharide vaccine [1]

1. Adults [is greater than or equal to] 65 yr old.

2. Adults, and children [is...

...lungs, diabetes, alcoholism, cirrhosis, cerebrospinal fluid leak, asplenia (including sickle cell disease), or nephrotic syndrome.

3. Adults, and children [is greater than or equal to] 2 yr old, who are immunocompromised...

...chronic renal failure, organ transplantation, asymptomatic or symptomatic human immunodeficiency virus).

Killed influenza virus [13]

1. High-risk groups in greatest need of vaccination: adults, and children [is greater than or...

...or anaemia, or immunosuppression children aged 6 mo to 8 yr on chronic aspirin therapy

3. Groups in whom vaccination should be considered: adults and children having extensive contact with high-risk patients adults providing essential community services

There is clear evidence that pneumococcus vaccine is effective in healthy young adults, [3] but there is debate about its effectiveness in high-risk groups. Two recent studies have found no benefit from vaccination in high-risk patients. [5,6] However, in the controlled trial [5] the randomisation seems to have been unsuccessful, [7] one of the end-points (bronchitis) was not specific to pneumococcal infection, and the study had only a 6% chance of detecting a vaccine efficacy of 65% for pneumococcal bacteraemia. [1] In the small case-control study [6] it is possible that some of the controls had, in fact, been vaccinated, and the selection of controls may have been biased. [1] On the other hand, five other studies have shown 60-70% vaccine efficacy in elderly patients in the United States and France. [1,8] In both of the negative studies, a high proportion of the elderly patients had...

...a good antibody response. [8] Against this, in healthy adults antibodies to most serotypes of pneumococcus return to prevaccination levels by 10 years after vaccination; [7] thus, much of the benefit...

...have been lost by 65. Local reactions are common in adults who are revaccinated within 1-2 years, but they are rare after 5 years. [1,7]

Fedson's review [7] suggests that there is a good response to pneumococcus vaccine in patients with diabetes, alcoholism, splenectomy without underlying immunosuppression, sickle-cell disease, and Hodgkin...

...than 2 years old have a poor antibody response to many of the serotypes in pneumococcus vaccine, and a high proportion of severe pneumococcal disease occurs in this age group. For otitis media in children, four studies have shown...
...shown benefit. [7] In the United States, vaccination is not recommended for recurrent otitis media. [1] A large randomised controlled trial of 14-valent vaccine in Papua New Guinea showed a highly significant 59% reduction of pneumonia as the sole cause of death in children younger than 5 years, and a just significant 50% reduction in children younger than 2 years (the age...vaccines in children under 2; furthermore, there was no bacteriological confirmation of the aetiology of pneumonia in this study, and the reduction in total mortality from pneumonia (alone or combined with other diseases) was not statistically significant in children vaccinated before they were 2 years old.

Improved pneumococcal vaccines

Children under 2 respond much better to vaccines in which the polysaccharide is conjugated to a protein, probably because the protein stimulates helper T cells. [3,4,7] Furthermore, children primed with a polysaccharide-protein conjugate vaccine get a booster response to revaccination with pure polysaccharide. Pneumococcal conjugate vaccines have been tested in adults, and studies in children are planned. [4] It may be difficult to produce a conjugate vaccine that includes more than 6-8 serotypes; types 4, 6, 9, 14, 18, 19F, and 23F have the highest priority for the prevention of otitis media in the United States, and types 1, 2, and 5, in addition to the above types, are important causes of pneumonia in developing countries.

Monoclonal antibodies to several pneumococcal surface proteins have been shown to protect mice against fatal pneumococcal infection, and attempts are being made to clone the genes that code for the surface proteins. Other approaches to immunisation against S pneumoniae include the use of aluminium phosphate as an adjuvant, [3] a hexasaccharide vaccine, [7] and a vaccine composed of monoclonal anti-idiotype antibodies. [7]

Influenza...

...example, in 1986, A/Leningrad/360/86 showed a moderate antigenic drift from A/Mississippi/1/85 isolated in 1985, but both viruses were subtype H3N2. Individuals previously infected with the...

...Whole-virus vaccines should not be used in children. Guillain-Barre syndrome developed in about 1 in 100 000 adults given the swine influenza vaccine in the United States in 1976...between vaccination and challenge, and in matching of vaccine and challenge antigens.

Hoskins et al [14] studied the effect of annual immunisation with killed vaccine for 7 years in a boarding...
...by means of recombinant DNA technology, synthesis of parts of the haemagglutinin molecule in vitro, conjugation of haemagglutinin to diphtheria toxoid, incorporation of the genes for haemagglutinin and neuraminidase into vaccinia virus, and use of adjuvants such as RV4170 (a glycoprotein from Klebsiella pneumoniae) and thymosin alpha one (a hormone from the thymus). [12,13]

Live influenza vaccines

Live...

...internal proteins in this virus, and the attenuation has been stable even in children. Phase 1 and 2 clinical trials have shown that cold-adapted Ann Arbor vaccines given intranasally produce...

...contribution to immunity (particularly in children). However, "take"-rates in seronegative volunteers given 10[6-5-7-0] [TCID.sub.50] doses of cold-adapted vaccine have been disappointing--antibody responses...

...infectionor whether such individuals are susceptible to natural infection (true vaccine failure). Large trials lasting 5 years are in progress to compare the efficacy of cold-adapted and killed influenza A... ...long duration because of the evidence that killed vaccines are less effective after repeated administration. [14,15] Phase 1 trials have shown that a cold-adapted influenza B vaccine is safe in man, and...

...avian-human influenza A vaccines is being assessed.

Conclusion

Cold-adapted live influenza vaccine and conjugate polysaccharide-protein pneumococcus vaccine should greatly improve our ability to prevent disease caused by these organisms. The impact...

...benefit analysis has shwon that there is an important role for the current vaccines against pneumococcus [17] and influenza [18,19] in developed countries--and yet they are grossly underutilised. The...

...annual revaccination and the evidence that there may be poor protection in those vaccinated regularly. Pneumococcus and influenza vaccines can be given at the same time, if injected at different sites...

...of discharge from hospital, at outpatient clinics, in general practice, and at chronic-care institutions. [1]

REFERENCES

[1] ACIP. Pneumococcal polysaccharide vaccine. MMWR 1989; 38: 64-77.

[2] Institute of Medicine. New vaccine development: establishing...

...Vol II, disease of importance in the United States. Washington DC: National Academy Press, 1985.

[3] Austrian R. Pneumococcal polysaccharide vaccines. Rev Infec Dis 1989; 11: S598-602.

[4] Anderson P, Betts R. Human adult immunogenicity of protein-coupled pneumococcal capsular antigens of serotypes prevalent in otitis media. Pediatr Infect Dis 1989; 8: S50-53.

[5] Simberkoff MS, Cross AP, Al-Ibrahim M, et al. Efficacy of pneumococcal vaccine in high-risk patients: results of a Veterans Administration cooperative study. N Engl F Med 1986; 315: 1318-27.

[6] Forrester HL, Jahnigen DW, LaForce FM. Inefficacy of pneumococcol vaccine in a high-risk population. Am F Med 1987; 83: 425-30.

[7] Fedson DS. Pneumococcal vaccine. In: Plotkin SA, Mortimer EA, eds. Vaccines. Philadelphia: WB Saunders, 1988: 271-99.

[8] LaForce FM, Eickhoff TC. Pneumococcal vaccine: an emerging consensus. Ann Intern Med 1988; 108: 757-59.

[9] Riley ID, Alpers MP, Gratten H, Lehmann D, Marshall TFDC, Smith D. Pneumococcal vaccine prevents death from acute lower-respiratory-tract infections in Papua New Guinean children. Lancet...

...Epidemiologic implications of changes in the influenza virus genome. Am F Med 1987; 82 (suppl 6A): 4-14.

[12] Murphy BR, Webster RG. Influenza viruses. In: Fields BN, ed. Virology. New York: Raven...

...influenza vaccines. In: Plotkin SA, Mortimer EA, eds. Vaccines. Philadelphia: WB Saunders, 1988: 420-34.
[14] Hoskins TW, Davies JR, Smith AJ, Miller CL, Allchin A. Assessment of inactivated influenza-A...

...88.
[17] Bolan G, Broome CV, Facklam RR, Plikaytis BD, Fraser DW, Schlech III WF. Pneumococcal vaccine efficacy in selected populations in the United States. Ann Intern Med 1986; 104: 1-6.
[18] Schoenbaum SC. Economic impact of influenza: the individual's perspective. Am F Med 1987; 82 (suppl 6A): 26-30.
[19] Helliwell BE, Drummond MF. The costs and benefits of preventing influenza in...

...DESCRIPTORS: Pneumonia, Pneumococcal--...

...Pneumococcal vaccine

14/3,K/37 (Item 1 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00130990

Effect of Pneumococcal Conjugate Vaccine on Pneumococcal Meningitis (Original Articles)

Hsu, Heather E.; Shutt, Kathleen A.; Moore, Matthew R.; Beall, Bernard W.; Bennett, Nancy M.; Craig, Allen S.; Farley, Monica M.; Jorgensen, James H.; Lexau, Catherine A.; Petit, Susan; Reingold, Arthur; Schaffner, William; Thomas, Ann; Whitney, Cynthia G.; Harrison, Lee H.
The New England Journal of Medicine
Jan 15, 2009; 360 (3),pp 244-256
LINE COUNT: 00474 WORD COUNT: 06544

Effect of Pneumococcal Conjugate Vaccine on Pneumococcal Meningitis (Original Articles)

Abstract
Background: Invasive pneumococcal disease declined among children and adults after the introduction of the pediatric heptavalent pneumococcal conjugate vaccine (PCV7) in 2000, but its effect on pneumococcal meningitis is unclear.
Methods: We examined trends in pneumococcal meningitis from 1998 through 2005 using active, population-based surveillance data from eight sites in the United States. Isolates were grouped into PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), PCV7-related serotypes (6A, 9A, 9L, 9N, 18A, 18B, 18F, 19B, 19C, 23A, and 23B), and non-PCV7 serotypes (all others). Changes in the incidence of pneumococcal meningitis were assessed against baseline values from 1998-1999.
Results: We identified 1379 cases of pneumococcal meningitis. The incidence declined from 1.13 cases to 0.79 case per 100,000 persons between 1998-1999 and 2004-2005 (a 30.1% decline, P<0.001). Among persons younger than 2 years of age and those 65...

...64.0% and 54.0%, respectively (P<0.001 for both groups). Rates of PCV7-serotype meningitis declined from 0.66 case to 0.18 case (a 73.

3% decline, P<0.001) among patients of all ages. Although rates of PCV7-related-serotype disease decreased by 32.1% (P=0.08), rates of non-PCV7-serotype disease increased from 0.32 to 0.51 (an increase of 60.5%, P<0.001). The percentages of cases from non-PCV7 serotypes 19A, 22F, and 35B each increased significantly during the study period. On average, 27.8% of isolates were nonsusceptible to penicillin, but fewer isolates were nonsusceptible to chloramphenicol (5.7%), meropenem (16.6%), and cefotaxime (11.8%). The proportion of penicillin-nonsusceptible isolates decreased between 1998 and 2003 (from 32.0% to 19.4%, P=0.01) but increased between 2003 and 2005 (from 19. 4% to 30.1%, P=0.03).

Conclusions: Rates of pneumococcal meningitis have decreased among children and adults since PCV7 was introduced. Although the overall effect...

TEXT

...Streptococcus pneumoniae is the most common cause of bacterial meningitis in the United States and many countries worldwide. (Ref. 1 -4) Despite effective antimicrobial therapy, pneumococcal meningitis remains highly lethal and has substantial long-term sequelae. (Ref. 4,5)

...

...The pediatric heptavalent pneumococcal conjugate vaccine (PCV7; Prevnar, Wyeth) has had a major effect on the incidence of pneumococcal disease in the United States. (Ref. 6) PCV7 not only protects immunized children from pneumococcal disease (Ref. 7-11) but also provides protection to nonimmunized children and adults through herd immunity, resulting from reduced transmission of S. pneumoniae from immunized children. (Ref. 8,10,12,13) Licensed in 2000, PCV7 is recommended by...

...and for children 24 to 59 months of age who are at increased risk for pneumococcal disease. (Ref. 14,15) In 2006, coverage by PCV7 among children 19 to 35 months of age was...

...A potential effect of decreasing vaccine serotypes in circulation is the emergence of non-PCV7 pneumococcal serotypes. However, in persons not infected with the human immunodeficiency virus (HIV), increases in the incidence of invasive pneumococcal disease from non-PCV7 serotypes have been minor relative to reductions in PCV7-serotype disease. (Ref. 9,17) The absence of substantial increases in rates of non-PCV7-serotype invasive disease, despite increased nasopharyngeal colonization with non-PCV7 serotypes, is presumably due to reduced invasive potential of some non-PCV7 serotypes. (Ref. 18) In contrast, increases in non-PCV7-serotype invasive disease among adults with HIV infection is substantial, probably reflecting the increased vulnerability of...

...Infections Programs Network, has conducted continuous, active, laboratory-based and population-based surveillance for invasive pneumococcal disease in eight states. (Ref. 19) In a previous analysis of Active Bacterial Core surveillance data on invasive pneumococcal disease for older adults, the incidence of meningitis in persons 50 years of age or...

...1998-1999 and 2002-2003, whereas there was a 57% reduction in the incidence of pneumococcal bacteremia without a known primary focus of infection. (Ref. 12) In separate studies of pneumococcal disease in infants and children, both the Active Bacterial Core surveillance network and the U.S. Pediatric Multicenter Pneumococcal Surveillance Study Group found substantial declines in the incidence of pneumococcal meningitis. (Ref. 8,20) Specifically, Whitney et al. (Ref. 8) found a 56% reduction in the incidence of pneumococcal meningitis in children under 24 months of age in 2001 as compared with the prelicensure...

...1994-2000 and 2002. To further investigate the effect of PCV7, we examined trends in pneumococcal meningitis among children and adults from 1998 through 2005...

...Case Ascertainment and Case Definitions
Active Bacterial Core surveillance conducts continuous active surveillance for invasive pneumococcal disease through regular contact with clinical microbiology laboratories at each site. (Ref. 19,21) Active...

...on demographic characteristics, clinical syndromes, and outcomes of illness are completed for each identified patient. Pneumococcal isolates are collected and sent to reference laboratories for serotyping and susceptibility testing...
...The case definition for pneumococcal meningitis was isolation of S. pneumoniae from cerebrospinal fluid or the clinical diagnosis of meningitis with pneumococcus isolated from another normally sterile site, usually blood. Only persons residing in Active Bacterial Core surveillance catchment areas were included.
Study Period and Population
We included patients with pneumococcal meningitis with culture dates from January 1, 1998, through December 31, 2005, occurring in eight Active Bacterial Core surveillance sites: California (San...

...area), Minnesota (a 7-county area), New York (the 7-county Rochester area), Oregon (the 3-county Portland area), and Tennessee (5 urban counties). In 2005, these surveillance areas represented an estimated 18,484,432 persons. (Ref...

...Serotype Groupings
Approximately 90 serotypes of S. pneumoniae have been identified on the basis of serologic properties of their polysaccharide capsule. We classified these pneumococci into one of three serotype groups. PCV7 serotypes were those that matched serotypes included in the vaccine (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F). PCV7-related serotypes were those within the same serogroup as the PCV7 serotypes that were either assumed or known to be cross-reactive with PCV7 serotypes (6A, 9A, 9L, 9N, 18A, 18B, 18F, 19B, 19C, 23A, and 23B). These designations were the same as those used in previous studies, (Ref. 25,26) with one exception. Serotype 19A was excluded from the group of PCV7-related serotypes because of evidence of lack of effectiveness of PCV7 against this serotype, (Ref. 26) as well as data indicating that PCV7 elicits nonfunctional antibodies in response to the 19A polysaccharide. (Ref. 27) All other serotypes, including 19A, were designated as non-PCV7 serotypes. All group classifications were made before data analysis began...

...serotypes were assigned, for purposes of incidence-rate calculations, on the basis of the known serotype distributions for a given year, age group, and race. If there were no known serotype distributions available for a particular age and race, then the missing serotypes were assigned on the basis of age group alone.
Statistical Analysis
We used SAS (version 9.1, SAS Institute) for data analysis. Rates of pneumococcal meningitis, expressed as the number of cases per 100,000 persons, were calculated with the...

...Because PCV7 was licensed in 2000, changes in the incidence of pneumococcal meningitis between 2-year periods were assessed by comparing the rates from periods after 1998...

...1998-1999 as relative risks. These risks are reported as the percent

changes (relative risk-1] x 100) in the rates between the two periods, together with the associated exact P...

...Results

We identified 1379 cases of pneumococcal meningitis during the study period (Table 1). The ages of the patients ranged from 2 days to 93 years. The median age...

...was 15 months and of the adults 53 years. The case fatality rate was 8.4% among children and 22.3% among adults.|*Table 1.-Characteristics of the Study Patients with 1379 Cases of Pneumococcal Meningitis at Eight Surveillance Sites, 1998-2005 *.**TABLE OMITTED...

...The adults with pneumococcal meningitis who were HIV-positive and those who were HIV-negative differed significantly with respect...

...age (median, 43 vs. 54 years; P<0.001), sex (male, 69.0% vs. 49.4%; P<0.001), and race (black, 71.0% vs. 26.7%; P<0.001). Case...

...the HIV-positive and HIV-negative adults (23.0% and 20.7%, P=0.83). Serotype groupings of isolates did not differ significantly according to HIV status of the patient.

Incidence of Pneumococcal Meningitis

Overall, rates of pneumococcal meningitis declined by 30.1% between the 1998-1999 baseline period and 2004-2005, from 1.13 cases to 0.79 case per 100,000 persons (P<0.001) (Table 2...

...rates decreased by 54.0% (P<0.001 for both comparisons). For those 2 to 4 years of age and 5 to 17 years of age, there were too few cases to make firm conclusions about...

...39 years of age, there was a decline in the rate of meningitis by 28.1% between 2004-2005 and 1998-1999 (P=0.10). In the analysis of trends in the percentage of case patients with underlying illness according to age and infective serotype (PCV7, PCV7-related, or non-PCV7), no significant trends were found.|*Table 2.-Mean Annual Incidence of Pneumococcal Meningitis at Eight Surveillance Sites, According to Age Group, Serotype Group, and Years (1998-2005) *.**TABLE OMITTED...

...PCV7-Serotype Disease

Among all age groups, the incidence of pneumococcal meningitis caused by PCV7 serotypes declined from 0.66 case per 100,000 persons in...

...1999 to 0.18 case per 100,000 in 2004-2005 (a decline of 73.3%, P<0.001) (Figure 1 and Table 2). In five of the six age groups examined, the incidence of PCV7-serotype meningitis declined significantly between 1998-1999 and 2004-2005 (Table 2), with the percent decreases...

...to 61.6% among persons who were 40 to 64 years of age. For patients 5 to 17 years of age, there were too few cases of PCV7-serotype disease to make meaningful conclusions.|*Figure 1.-Mean Annual Incidence of Pneumococcal Meningitis, According to Serotype Group and Time Period.Serotypes of the heptavalent pneumococcal conjugate vaccine (PCV7) were 4, 6B, 9V, 14, 18C, 19F, and 23F. PCV7-related serotypes were 6A, 9A, 9L, 9N, 18A, 18B, 18F, 19B, 19C, 23A, and 23B. Non-PCV7 serotypes were 3, 7F, 10A, 11A, 12F, 15A, 15B/C, 16F, 19A, 22F, 33F, 35B, 35F, and 38 *.**FIGURE OMITTED...

...PCV7-Related-Serotype Disease

Rates of PCV7-related-serotype disease declined by 32.1% between 1998-1999 and 2004-2005, from 0.14 case to 0.10 case per

100,000 persons for all age groups (P=0.08). In addition to the significant 83.5% decline in the rate of PCV7-related cases within the vaccine's target population (children...

...Non-PCV7-Serotype Disease

For all age groups, rates of non-PCV7-serotype disease increased significantly from 0.32 case to 0.51 case per 100,000 persons from 1998-1999 to 2004-2005 (an increase of 60.5%, P<0.001). Although this increase was driven mostly by a relative increase of 275...

...2 years of age (P=0.001), significant increases in the rate of non-PCV7-serotype meningitis were also found among children 2 to 4 years of age (P=0.001) and adults 40 to 64 years (an increase of 68.1%, P=0.005). A nonsignificant increase of 75.6% in the rate of non-PCV7...

...PCV7 serotypes among adults, we conducted a separate analysis of the incidence of non-PCV7-serotype disease, excluding all 100 patients who were known to be HIV-positive. In the HIV-negative subgroup, from 1998-1999 to 2004-2005, the incidence of non-PCV7-serotype disease increased from 0.14 case to 0.24 case per 100,000 persons for adults 18 to 39 years of age (an increase of 67.1%, P=0.15) and from 0.41 case to 0.54 case per 100,000...

...We also examined trends in the incidence of pneumococcal meningitis caused by specific non-PCV7 strains. From 1998-1999 to 2004-2005, the rate of disease from serotype 19A increased from 0.02 case to 0.08 case per 100,000 persons (P<0.001), and the rate of disease from the 22F serotype increased from 0.03 to 0.08 per 100,000 persons (P=0.003). Rates...

...by Specific Serotypes

The proportion of total cases caused by non-PCV7 serotypes 11A, 16F, 19A, 22F, and 35B increased significantly between 1998-1999 and 2004-2005 (Table 3). The increases associated with serotypes 19A and 22F were particularly notable: serotype 19A represented 1.5% (5 cases) of the total number in 1998-1999, but 11.1% (28 cases) in 2004-2005 (P<0.001). Likewise, the percentage of the total number of cases that were due to serotype 22F increased from 2.4% (8 cases) in 1998-1999 to 10.3% (26 cases) in 2004-2005 (P<0.001).|*Table 3.-Distribution of 1239 Cases of Pneumococcal Meningitis, 1998-2005, According to Serotype Grouping *.**TABLE OMITTED**

Estimated Coverage by Vaccines in Development

Currently, both 10-valent and 13-valent pneumococcal conjugate vaccines (PCV10 and PCV13, respectively) are in phase 3 clinical trials. (Ref. 29,30) PVC10 includes, in addition to the PCV7 serotypes, serotypes 1, 5, and 7F and would have covered 27.4% of cases in 2004-2005. PCV13, which includes the PCV10 types plus serotypes 3, 6A, and 19A, would have covered 50.0% of cases in that year.

Antibiotic Susceptibility

The incidence of...

...nonsusceptible to penicillin, meropenem, or cefotaxime decreased significantly between 1998-1999 and 2004-2005 (Table 4). Trends in disease caused by isolates nonsusceptible to chloramphenicol were not examined because of the small number of these isolates. Overall, 27.8% of isolates were nonsusceptible to penicillin, 5.7% to chloramphenicol, 16.6% to meropenem, and 11.8% to cefotaxime (Table 1 in the Supplementary Appendix). In 2004-2005, the percentages of isolates that were of intermediate susceptibility and resistant to penicillin were 17.5% and 9.9%, respectively; to chloramphenicol, 0.0% and 4.4%; to meropenem, 4.0% and 7.5%; and to cefotaxime, 6.

3% and 2.8%.|*Table 4.-Mean Annual Incidence of Pneumococcal Meningitis at Eight Surveillance Sites, According to Age Group, Antibiotic Susceptibility, and Years (1998-2005...

...susceptible to levofloxacin and rifampin. A total of 40.8% of PCV7 isolates and 33.1% of PCV7-related isolates were nonsusceptible to penicillin. Lower percentages of PCV7-serotype isolates were nonsusceptible to chloramphenicol, meropenem, and cefotaxime (8.4%, 28.0%, and 20.3%, respectively). Similarly, the percentage of PCV7-related and non-PCV7 isolates that were nonsusceptible to chloramphenicol, meropenem, or cefotaxime did not exceed 14.9%. Although we found relatively low levels of nonsusceptibility to penicillin among non-PCV7 isolates overall (12.4%), decreased susceptibility was common among isolates of serotypes 15A (62.5%), 19A (60.7%), and 35B (69.6...

...and P=0.01, respectively) (Fig. 1C in the Supplementary Appendix).|*Figure 2.-Percentage of Pneumococcal Isolates, from 1239 Cases, That Were Nonsusceptible to Various Antibiotics, According to Year and Degree of Nonsusceptibility.For 1998-2005, 140 isolates lacking serotype or susceptibility data were excluded. The total number of isolates tested was 147 in 1998...
...Discussion

These data show that the overall rates of pneumococcal meningitis decreased substantially from 1998-1999 to 2004-2005. Similar to earlier studies, (Ref. 8...

...younger than 2 years of age. We also found that the incidence of both PCV7-serotype disease and PCV7-related-serotype disease decreased significantly, by 73% and 32%, respectively, among all patients. The incidence of PCV7-serotype disease decreased significantly in all but one of the age groups examined, whereas the incidence...

...years of age and those 65 years of age or older. Rates of non-PCV7-serotype disease increased significantly, by 61%, during the study period. Although the rise in non-PCV7 disease was primarily driven by an increase in non-PCV7-serotype disease in the vaccine's target population, children younger than 2 years of age, the...

...10 cases per 100,000 persons) was small relative to the corresponding decrease in PCV7-serotype disease (7.61 cases per 100,000 persons...

...of young children with PCV7 has caused significant declines in the incidence of all invasive pneumococcal disease, not only in the age group targeted but also among older children and adults. (Ref. 7-10,12) The current study confirms that this effect holds for pneumococcal meningitis, especially for children younger than 2 years of age and adults 65 years of...

...Recently, Whitney et al. (Ref. 26) examined the effectiveness of PCV7 for various pneumococcal serotypes in a case-control study. They found that the effectiveness of one or more doses of vaccine against disease caused by a vaccine serotype was 96% in healthy children; the effectiveness against meningitis in particular was also 96%. For serotypes within the same serogroup as the vaccine types, the effectiveness against serotype 6A was approximately 75%, and there was no evidence of protection against serotype 19A. Although we did not find any significant change in the rate of meningitis from serotype 6A overall, we did find that the rate of meningitis from serotype 19A increased significantly during the study period, supporting the lack of vaccine effectiveness against this serotype. One explanation for the apparent lack of reduction in the rate of pneumococcal meningitis caused by serotype 6A is that some of the isolates

classified as 6A may actually be 6C, a newly identified serotype that cannot be distinguished from 6A by means of standard serotyping. (Ref. 31...
...Several studies of pneumococcal disease found that rates of antibiotic-resistant invasive pneumococcal disease declined in both young children and older persons after the introduction of PCV7. (Ref...

...25,32) This observation is most likely due to the fact that the introduction of conjugate vaccines has led to a reduction in the rates of nasopharyngeal carriage of, and disease...

...Ref. 33) Likewise, in the current study, we found a substantial decline in incidence of pneumococcal meningitis due to serotypes that are nonsusceptible to antibiotics, indicating a strong public health effect...

...have predicted that high levels of exposure to antibiotics may limit the success of the pneumococcal conjugate vaccine. (Ref. 34...

...In addition, antibiotic resistance remains a serious concern for physicians treating pneumococcal meningitis, since relatively few available drugs can attain therapeutic concentrations in cerebrospinal fluid. Despite the decrease in incidence of nonsusceptible pneumococcal meningitis, we observed a recent resurgence in the proportion of nonsusceptible isolates among the remaining cases, which has implications for empirical therapy for pneumococcal meningitis. We also found that although nonsusceptibility to penicillin occurs mostly among PCV7-serotype isolates, the percentages of isolates of several non-PCV7 serotypes that are nonsusceptible to penicillin...

...Our data provide strong evidence of the benefit of PCV7 in reducing rates of pneumococcal meningitis, including those caused by strains nonsusceptible to antimicrobial agents. Decreases in disease rates represent...

...immunized population as well as an indirect benefit resulting from decreased transmission of PCV7-type pneumococci from immunized children to nonimmunized children and adults. Despite these decreases, the recent increase in the proportion of pneumococcal meningitis isolates that are nonsusceptible to antimicrobial agents indicates that antimicrobial resistance is a clinical...

...PCV7 serotypes indicate the need for continued development of more broadly protective vaccines. Given that pneumococcal meningitis remains highly lethal, with approximately 1 in 12 cases in children and 1 in 5 cases in adults resulting in death in our study, additional prevention measures are needed...
...Bennett, honoraria and travel expenses from Wyeth for an advisory board meeting on an experimental pneumococcal vaccine and from Merck for participation on an advisory board on herpes zoster vaccine; Dr...

...and safety monitoring board for experimental vaccines and advisory-board meetings on adult immunization and pneumococcal vaccine; and Dr. Harrison, consulting fees and honoraria from Wyeth, Merck, Sanofi-Pasteur, and GlaxoSmithKline

CITED REFERENCES
|^\1
1. Bingen E, Levy C, Varon E, et al. Pneumococcal meningitis in the era of pneumococcal conjugate vaccine implementation. Eur J Clin Microbiol Infect Dis 2008;27:191-9.
2. Schuchat A...

...meningitis in the United States in 1995. N Engl J Med 1997;337:970-6.

3. Thigpen MC, Rosenstein N, Whitney CG, et al. Bacterial meningitis in the United States -- 1998...

...Annual Meeting of the Infectious Disease Society of America, San Francisco, October 6-9, 2005.
4. Dery M, Hasbun R. Changing epidemiology of bacterial meningitis. Curr Infect Dis Rep 2007;9:301-7.
5. Neuman HB, Wald ER. Bacterial meningitis in childhood at the Children's Hospital of Pittsburgh: 1988-1998. Clin Pediatr (Phila) 2001;40:595-600.
6. Musher DM. Pneumococcal vaccine -- direct and indirect (``herd'') effects. N Engl J Med 2006;354:1522-4.
7. Poehling KA, Talbot TR, Griffin MR, et al. Invasive pneumococcal disease among infants before and after introduction of pneumococcal conjugate vaccine. JAMA 2006;295:1668-74.
8. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. N Engl J Med 2003;348:1737-46.
9. Flannery B, Schrag S, Bennett NM, et al. Impact of childhood vaccination on racial disparities in invasive Streptococcus pneumoniae infections. JAMA 2004;291:2197-203.
10. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease -- United States, 1998-2003. MMWR Morb Mortal Wkly Rep 2005;54:893-7.
11. Black S, France EK, Isaacman D, et al. Surveillance for invasive pneumococcal disease during 2000-2005 in a population of children who received 7-valent pneumococcal conjugate vaccine. Pediatr Infect Dis J 2007;26:771-7.
12. Lexau CA, Lynfield R, Danila R, et al. Changing epidemiology of invasive pneumococcal disease among older adults in the era of pediatric pneumococcal conjugate vaccine. JAMA 2005;294:2043-51.
13. Flannery B, Heffernan RT, Harrison LH, et al. Changes in invasive pneumococcal disease among HIV-infected adults living in the era of childhood pneumococcal immunization. Ann Intern Med 2006;144: 1-9.
14. Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2000;49(RR-9):1-35.
15. American Academy of Pediatrics, Committee on Infectious Diseases. Policy statement: recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. Pediatrics 2000;106:362-6.
16. Immunization coverage in the...

...Q1/2006-Q4/2006.)
17. Hicks LA, Harrison LH, Flannery B, et al. Incidence of pneumococcal disease due to non-pneumococcal conjugate vaccine (PCV7) serotypes in the United States during the era of widespread PCV7 vaccination, 1998...

...Meats E, Peto T, Crook DW, Spratt BG. Clonal relationships between invasive and carriage Streptococcus pneumoniae and serotype - and clone-specific differences in invasive disease potential. J Infect Dis 2003;187:1424-32...

...htm#background.)
20. Kaplan SL, Mason EO Jr, Wald ER, et al. Decrease of invasive pneumococcal infections in children among 8 children's hospitals in the United States after the introduction of the 7-valent

pneumococcal conjugate vaccine. Pediatrics 2004;113:443-9.
21. Active Bacterial Core surveillance (ABCs) report: Emerging Infections Program Network: Streptococcus pneumoniae, 2005 -- provisional. Atlanta: Centers for Disease Control and Prevention, 2006. (Accessed December 18, 2008, at...

...84.
25. Kyaw MH, Lynfield R, Schaffner W, et al. Effect of introduction of the pneumococcal conjugate vaccine on drug-resistant Streptococcus pneumoniae. N Engl J Med 2006;354:1455-63. Erratum, N Engl J Med 2006;355:638.]
26. Whitney CG, Pilishvili T, Farley MM, et al. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. Lancet 2006;368:1495-502.
27. Yu X, Gray...

...Chang S, Ward JI, Edwards KM, Nahm MH. Immunity to cross-reactive serotypes induced by pneumococcal conjugate vaccines in infants. J Infect Dis 1999;180:1569-76.
28. National Vital Statistics System...

...about/major/dvs/popbridge/datadoc.htm.)
29. ClinicalTrials.gov. Safety & immunogenicity study of 10-valent pneumococcal conjugate vaccine when administered as a 2-dose schedule. Rockville, MD: National Institutes of Health, 2006...

...18, 2008, at http://clinicaltrials.gov/ct2/show/NCT00307034.)
30. Idem. Study evaluating 13-valent pneumococal conjugate vaccine in healthy infants. Rockville, MD: National Institutes of Health, 2007. (Accessed December 18, 2008...

...Pritchard DG, Cartee R, Brandao A, Brandileone MC, Nahm MH. Discovery of a new capsular serotype (6C) within serogroup 6 of Streptococcus pneumoniae. J Clin Microbiol 2007;45:1225-33.
32. Talbot TR, Poehling KA, Hartert TV, et al. Reduction in high rates of antibiotic-nonsusceptible invasive pneumococcal disease in Tennessee after introduction of the pneumococcal conjugate vaccine. Clin Infect Dis 2004;39:641-8.
33. Dagan R, Givon-Lavi N, Zamir O, Fraser D. Effect of a nonavalent conjugate vaccine on carriage of antibiotic-resistant Streptococcus pneumoniae in day-care centers. Pediatr Infect Dis J 2003;22:532-40.
34. Temime L, Boelle PY, Valleron AJ, Guillemot D. Penicillin-resistant pneumococcal meningitis: high antibiotic exposure impedes new vaccine protection. Epidemiol Infect 2005;133:493-501.

14/3,K/38 (Item 2 from file: 444)
DIALOG(R)File 444:New England Journal of Med.

00123662

Decline in Invasive Pneumococcal Disease after the Introduction of Protein-Polysaccharide Conjugate Vaccine (Original Articles)

Whitney, Cynthia G.; Farley, Monica M.; Hadler, James; Harrison, Lee H.; Bennett, Nancy M.; Lynfield, Ruth; Reingold, Arthur; Cieslak, Paul R.; Pilishvili, Tamara; Jackson, Delois; Facklam, Richard R.; Jorgensen, James H.; Schuchat, Anne; for the Active Bacterial Core Surveillance of the Emerging Infections Program Network.

The New England Journal of Medicine
May 1, 2003; 348 (18),pp 1737-1746
LINE COUNT: 00366 WORD COUNT: 05061

Decline in Invasive Pneumococcal Disease after the Introduction of Protein-Polysaccharide Conjugate Vaccine (Original Articles)

Abstract

Background: In early 2000, a protein-polysaccharide conjugate vaccine targeting seven pneumococcal serotypes was licensed in the United States for use in young children.

Methods: We examined...

...Prevention to evaluate changes in the burden of invasive disease, defined by isolation of Streptococcus pneumoniae from a normally sterile site. Serotyping and susceptibility testing of isolates were performed. We assessed...

...population, 16 million).

Results: The rate of invasive disease dropped from an average of 24.3 cases per 100,000 persons in 1998 and 1999 to 17.3 per 100,000 in 2001. The largest decline was in children under two years of...

...for those 40 to 64 years of age (19.7 per 100,000 vs. 21.5 per 100,000, P=0.03), and 18 percent lower for those 65 years of age or more (49.5 per 100,000 vs. 60.1 per 100,000, P<0.001). The rate of disease caused by strains that were not susceptible to penicillin was 35 percent lower in 2001 than in 1999 (4.1 cases per 100,000 vs. 6.3 per 100,000, P<0.001).

Conclusions: The use of the pneumococcal conjugate vaccine is preventing disease in young children, for whom the vaccine is indicated, and may...

TEXT

...In early 2000, a 7-valent protein-polysaccharide pneumococcal conjugate vaccine (Prevnar, Wyeth Lederle Vaccines) was licensed for use in infants and young children in the United States. This was the first vaccine that promised efficacy against pneumococcal disease for this high-risk group. In the second half of 2000, recommendations for routine...

...age and in high-risk children two through four years of age were published, (Ref. 1,2) and distribution of the vaccine through public programs began. By August 2001, a shortage was reported. (Ref. 3)

...

...given as a four-dose regimen to infants, is highly efficacious against invasive disease (Ref. 4) and somewhat efficacious against otitis media (Ref. 4,5) and pneumonia. (Ref. 6) Conjugate vaccines reduce nasopharyngeal carriage of vaccine-type strains but often increase the frequency of carriage...

...in older children is unknown. Because the vaccine does not include most of the 90 pneumococcal serotypes, an increase in disease caused by serotypes not included in the vaccine or not...
...this effect was seen during a clinical trial evaluating its efficacy against otitis media. (Ref. 5) Whether vaccination of young children will reduce carriage and subsequently affect disease in other age...

...Network of the CDC, is an active, population-based, laboratory-based surveillance system. Between January 1, 1996, and December 31, 2001, the Active Bacterial Core Surveillance continuously monitored invasive pneumococcal infections in Portland, Oregon (three counties); San

Francisco County, California; Minneapolis and St. Paul, Minnesota...

...A case of invasive pneumococcal disease was defined by the isolation of Streptococcus pneumoniae from a sample of normally sterile body fluid taken from a surveillance-area resident. To...

...Pneumococcal isolates were sent to reference laboratories for serotyping by the quellung reaction. Isolates from Minnesota...

...of Health, and all others were tested at the CDC. Vaccine-type strains included serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F. We defined vaccine-related strains as pneumococci with serotypes within the same serogroup as the vaccine types (6A, 9A, 9L, 9N, 18A, 18B, 18F, 19A, 19B, 19C, 23A, and 23B). All other serotypes were considered nonvaccine types. Serotypes in the 23-valent polysaccharide vaccine but not in the conjugate vaccine included 1, 2, 3, 5, 7F, 8, 10A, 11A, 12F, 15B, 20, 22F, and 33F...years; the rates for 2000 and 2001 were calculated from 2000 Census data. To calculate serotype-specific disease rates, we assumed that the distribution of serotypes for cases with missing serotype data (11.7 percent of cases) was the same as the distribution for cases with serotype information available. The same method was used to impute missing data on race (11.0...

...analyses were conducted with SAS, version 8.0, and Epi Info, version 6.0, (Ref. 14) software. We calculated 95 percent confidence intervals, and two-sided P values that were less...

...During the period from 1998 through 2001, a total of 13,568 cases of invasive pneumococcal disease were identified; isolates were available for 11,992 (88 percent). The rates of invasive disease in 1998, 1999, 2000, and 2001 were 24.2, 24.4, 21.2, and 17.3 cases per 100,000 persons, respectively. The average for the base-line period of 1998 and 1999 was 24.3 per 100,000.

Children under Five Years of Age

From 1998 through 2001, 3285 cases of invasive pneumococcal disease were identified in children under five years of age. The rate declined by 59 percent (95 percent confidence interval, 54 to 63 percent), from an average of 96.4 cases per 100,000 in 1998 and 1999 to 39.7 per 100,000 in...

...in 2001, as compared with 188.0 per 100,000 in 1998 and 1999) (Figure 1). As compared with the base-line values for 1998 and 1999 combined, the rates of disease in 2000 were 17 percent lower among children under 12 months old (139.3 cases per 100,000 vs. 168.1; 95 percent confidence interval, 5 to 28 percent) and 27 percent lower among children 12 to 23 months old (152...

...interval, 17 to 35 percent); by 2001, the disease rates were 69 percent lower (52.3 cases per 100,000 vs. 168.1; 95 percent confidence interval, 62 to 75 percent) and 68 percent lower (65.8 vs...

...in 2001 than in 1998 and 1999 (35.6 cases per 100,000 vs. 63.3; 95 percent confidence interval, 27 to 56 percent). For children who were three or four...

...age, the rates in 2001 were not significantly different from the base-line values.|*Figure 1.-Rates of Invasive Pneumococcal Disease among Children under Five Years Old, According to Age and Year.Data are from...percent change in the rate of disease treated without hospitalization (from 132.7 to 38.1, a decline of 71 percent). Likewise, the percent change in the rate of pneumococcal meningitis (from 10.3 cases per 100,000 to 4.2, a decline of 59 percent)

was similar to that for the rate of other syndromes (from 179.4 to 55.8, a decline of 69 percent). The percent change in the rate of...

...2 to 61 percent) (Figure 2).|*Figure 2.-Percent Changes in the Rates of Invasive Pneumococcal Disease, According to Age Group and the State in Which the Active Bacterial Core Surveillance...

...significant declines in disease were seen for all individual serotypes included in the vaccine (Table 1). As compared with base line, the rate of disease due to vaccine-related strains as...

...serotypes was 27 percent higher in 2001, but this change was not statistically significant.|*Table 1.-Changes in Estimated Rates of Invasive Pneumococcal Disease among Children under Two Years of Age, According to Year and Serotype, from 1998 through 2001 *.**TABLE OMITTED**

Persons Five Years of Age or Older

Disease rates also fell among persons for whom the vaccine is not recommended (Figure 3). Although no significant change was observed among persons 5 through 19 years of age, the rate of disease among persons 20 through 39 years...

...declines were noted in disease caused by some individual serotypes included in the vaccine, particularly 4, 9V, 14, and 19F. Within surveillance sites, the size of the decline among persons 20 to 39 ...

...cases in persons without known HIV infection or AIDS dropped by 38 percent, from 270.5 in 1998 and 1999 to 168.0 in 2001; there was no significant change in...

...an average of 81 cases in 1998 and 1999 and 82 cases in 2001).|*Figure 3.-Rates of Invasive Pneumococcal Disease among Persons at Least Five Years Old, According to Age Group and Year.Data...

...rate for 1998 and 1999 *.**FIGURE OMITTED**|*Table 2.-Changes in Estimated Rates of Invasive Pneumococcal Disease among Adults, According to Age Group, Year, and Serotype, from 1998 through 2001 *.**TABLE OMITTED...

...in 2001 than in 1998 and 1999 (19.7 cases per 100,000 vs. 21.5; 95 percent confidence interval, 1 to 15 percent; P=0.03) (Figure 3). The change in the overall rate of disease in this age group was primarily due...

...serotypes included in the vaccine, only the change in the rate of disease due to serotype 14 was statistically significant...

...the rate of disease was 18 percent lower in 2001 than at base line (49.5 cases per 100,000 vs. 60.1; 95 percent confidence interval, 11 to 24 percent; P<0.001) (Figure 3). The rates were lower for disease caused by vaccine serotypes and vaccine-related serotypes; significant declines were seen for disease caused by vaccine serotypes 4, 9V, 14, and 23F (Table 2). The rate of disease caused by serotypes included in the 23-valent polysaccharide vaccine and not in the conjugate vaccine was the same in 2001 as in 1998 and 1999 (11.9 cases per...

...Among nonvaccine serotypes, the rate of serotype 1 disease was lower in some adult age groups in 2001 than in 1998 and 1999: for those between 40 and 64 years old, the rate declined from 0.5 to 0.1 case per 100,000 (P<0.001), and for those 65 years of age or older, the rate declined from 0.7 to 0.3 (P=0.05). The rate of serotype 5 disease was higher in 2001 than in 1998 and 1999 among persons 20

to 39...

...but this change was attributable to an increase in the number of cases caused by serotype 5 in one surveillance site (California), which had 1 isolate in 1998 and 1999 and 14 isolates in 2001.

Drug-Resistant Invasive Disease

The proportion of isolates that were not susceptible...

...penicillin and 15 percent were resistant; in 2001, 10 percent were of intermediate susceptibility and 14 percent were resistant. Between 1999 and 2001, the change in the rate of disease caused by strains that were not susceptible to penicillin (from 6.3 to 4.1, a decline of 35 percent; 95 percent confidence interval, 28 to 41 percent; P<0...

...from the change in the rate of disease caused by penicillin-susceptible strains (from 18.1 to 13.1, a decline of 28 percent; 95 percent confidence interval, 23 to 31 percent...

...20.9; 95 percent confidence interval, 62 to 77 percent) and 67 percent (from 115.5 to 38.5; 95 percent confidence interval, 60 to 72 percent), respectively. The rate of disease due to...

...Discussion

The use of the pneumococcal conjugate vaccine has reduced the burden of invasive disease in young children, for whom the vaccine...

...serotypes, as was seen in a clinical trial evaluating its efficacy against otitis media. (Ref. 5)

...among older children. These findings are consistent with recommendations for the use of vaccine (Ref. 1,2) and reported patterns of vaccine use (Ref. 3); data on vaccine coverage are not yet available. The manufacturer sold 9 million doses in 2000 and 15.5 million doses in 2001; less than 10 percent of private-sector sales were for children two years old or more (Paradiso P, Wyeth Lederle Vaccines: personal communication). Approximately 4 million children are born in the United States annually; therefore, 32 million doses would have been required to provide the 4-dose infant series for children born in 2000 and 2001, and millions more would have...

...through four years of age who had conditions that put them at high risk for pneumococcal infection. Although they are estimates, these figures suggest that changes in disease rates are occurring...

...protection with less than the full number of recommended doses and through decreased transmission of pneumococci between children...

...is noteworthy. Although young children have the highest risk of invasive disease, most cases of pneumococcal disease and nearly all deaths from pneumococcal disease occur in adults. (Ref. 16) Much of the change we observed in adults may be due to decreased transmission of pneumococci from children. Children are a reservoir for pneumococci; contact with young children in the household is a risk factor for invasive disease in...

...nasopharyngeal carriage is higher in adults with young children than in other adults. (Ref. 19) Conjugate vaccines have been shown to reduce the carriage of vaccine-type strains in vaccinated children...

...Multidrug-resistant pneumococci are a worldwide problem. In response, programs have been developed to reduce antimicrobial use. (Ref. 20,21) Our data indicate that conjugate vaccine is another effective tool for preventing infections caused by drug-resistant strains; 35 percent

...
...to penicillin-nonsusceptible strains occurred in 2001 than in 1999. Resistance is closely linked to pneumococcal serotype; in 1998, three fourths of penicillin-nonsusceptible pneumococci were of serotypes that were included in the vaccine, although pneumococci of common serotypes that were included in the vaccine, such as 4 and 18C, were rarely drug-resistant. (Ref. 22) Because the vaccine prevented a similar amount of disease caused by penicillin-susceptible and penicillin-nonsusceptible strains, the proportion of pneumococci with decreased susceptibility to penicillin did not change substantially...

...of the observations. However, we found no change in the rate of disease caused by pneumococci with serotypes unique to the polysaccharide vaccine or in the number of cases in persons...

...the rate of disease among children was similar for hospitalized patients and outpatients and for pneumococcal meningitis and other syndromes, suggesting that changes in culturing practices did not explain the observed
...

...Preventing pneumococcal disease is a priority for the United States. The Healthy People 2010 objectives include decreasing the incidence of invasive pneumococcal infections to 46 cases per 100,000 persons under 5 years of age and to 42 per 100,000 persons 65 years of age or
...

...will fall as vaccine coverage increases and to assess the effect of the vaccine on pneumonia and other noninvasive syndromes. Whether vaccine use will slow the emergence of resistant pneumococci and whether disease due to pneumococci with nonvaccine serotypes will become more common are questions that do not yet have definitive answers. Although questions remain, our data indicate that the pneumococcal conjugate vaccine is working well in the U.S. population...and Chemotherapy, Chicago, December 16-19, 2001 (abstract G-2041); the 3rd International Symposium on Pneumococci and Pneumococcal Diseases, Anchorage, Alaska, May 5-8, 2002; and the 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy, San Diego, Calif...

CITED REFERENCES
|^\1
1. Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep 2000;49(RR-9):1-35.
2. American Academy of Pediatrics, Committee on Infectious Diseases. Policy statement: recommendations for the prevention of pneumococcal infections, including the use of pneumococcal conjugate vaccine (Prevnar), pneumococcal polysaccharide vaccine, and antibiotic prophylaxis. Pediatrics 2000;106:362-6.
3. Updated recommendations on the use of pneumococcal conjugate vaccine in a setting of vaccine shortage -- Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep 2001;50:1140-2.
4. Black S, Shinefield H, Fireman B, et al. Efficacy, safety and immunogenicity of heptavalent pneumococcal conjugate vaccine in children. Pediatr Infect Dis J 2000;19:187-95.
5. Eskola J, Kilpi T, Palmu A, et al. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. N Engl J Med 2001;344:403-9.
6. Black SB, Shinefield HR, Ling S, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. Pediatr Infect Dis J 2002;21:810-5.
7. Mbelle N, Huebner RE, Wasas AD, Kimura A, Chang I, Klugman KP.

Immunogenicity and impact on nasopharyngeal carriage of a nonavalent pneumococcal conjugate vaccine. J Infect Dis 1999;180:1171-6.
8. Obaro SK, Adegbola RA, Banya WAS, Greenwood BM. Carriage of pneumococci after pneumococcal vaccination. Lancet 1996;348:271-2.
9. Obaro SK, Adegbola RA, Chang I, et al. Safety and immunogenicity of a nonavalent pneumococcal vaccine conjugated to CRM(sub 197) administered simultaneously but in a separate syringe with diphtheria, tetanus and...

...9.
10. Dagan R, Melamed R, Muallem M, et al. Reduction of nasopharyngeal carriage of pneumococci during the second year of life by a heptavalent conjugate pneumococcal vaccine. J Infect Dis 1996;174:1271-8.
11. Dagan R, Muallem M, Melamed R, Leroy O, Yagupsky P. Reduction of pneumococcal nasopharyngeal carriage in early infancy after immunization with tetravalent pneumococcal vaccines conjugated to either tetanus toxoid or diphtheria toxoid. Pediatr Infect Dis J 1997;16:1060-4.
12. Dagan R, Givon-Lavi N, Zamir O, et al. Reduction of nasopharyngeal carriage of Streptococcus pneumoniae after administration of a 9-valent pneumococcal conjugate vaccine to toddlers attending day care centers. J Infect Dis 2002;185:927-36.
13...

...NCCLS document M100-S12. Vol. 22. Wayne, Pa.: National Committee for Clinical Laboratory Standards, 2002.
14. Dean AG, Dean JA, Coulombier D, et al. Epi Info, version 6: a word processing...

...J, Elvin L, Laufer D, Malinoski F. Postlicensure evaluation of the effectiveness of seven valent pneumococcal conjugate vaccine. Pediatr Infect Dis J 2001;20:1105-7.
16. Robinson KA, Baughman W, Rothrock G, et al. Epidemiology of invasive Streptococcus pneumoniae infections in the United States, 1995-1998: opportunities for prevention in the conjugate vaccine era. JAMA 2001;285:1729-35.
17. Breiman RF, Keller DW, Phelan MA, et al. Evaluation of effectiveness of the 23-valent pneumococcal capsular polysaccharide vaccine for HIV-infected patients. Arch Intern Med 2000;160:2633-8.
18. Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease. N Engl J Med 2000;342:681-9.
19. Hendley JO, Sande MA, Stewart PM, Gwaltney JM Jr. Spread of Streptococcus pneumoniae in families. I. Carriage rates and distribution of types. J Infect Dis 1975;132:55...

...use of antimicrobial agents for pediatric upper respiratory tract infections. Pediatrics 1998;101:Suppl:163-5.
21. Gonzales R, Bartlett JG, Besser RE, et al. Principles of appropriate antibiotic use for...

...22. Whitney CG, Farley MM, Hadler J, et al. Increasing prevalence of multidrug-resistant Streptococcus pneumoniae in the United States. N Engl J Med 2000;343:1917-24.
23. Department of...
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Set	Items	Description
S1	85	E1-E8
S2	20	S1 AND (VALENT OR SEROTYPE)
S3	15	RD (unique items)

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S4        166   E1-E6
S5         18   S4 AND (VALENT OR SEROTYPE)
S6          9   RD  (unique items)
S7         77   E1-E6
S8         18   S7 AND (SEROTYPE OR VALENT)
S9         13   RD  (unique items)
S10      1964   SEROTYPE AND (6A)
S11     26417   SEROTYPE AND PNEUM?
S12      7610   S11 AND (CONJUGAT?)
S13        58   S12 AND (1 AND 3 AND 4 AND 5 AND 6A AND 6B AND 7F AND 9V A-
               ND 14 AND 18C AND 19A AND 23F)
S14        38   RD  (unique items)



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E1        6  AU=PARADISO, P.
E2       28  AU=PARADISO, P. R.
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E4        3  AU=PARADISO, PETER R
E5       30  AU=PARADISO, PETER R.
E6        1  AU=PARADISO, PETER ROCCO
E7       26  AU=PARADISO, PR
E8        2  AU=PARADISO, R
E9      106  AU=PARADISO, R.
E10       2  AU=PARADISO, R. A.
E11       2  AU=PARADISO, R. L.
E12       1  AU=PARADISO, RICHARD
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E16       7  AU=PARADISO, S.
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E19       1  AU=PARADISO, S.N.
E20       1  AU=PARADISO, SAM J.
E21      12  AU=PARADISO, SERGIO
E22       4  AU=PARADISO, SERGIO, M.D., PH.D.
E23       1  AU=PARADISO, SHARON DESMOND
E24       1  AU=PARADISO, T.
E25       1  AU=PARADISO, T. J.
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            6   AU=PARADISO, P.
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S2          9   S S1 AND SACCHARIDE

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>>>W:  KWIC option is not available in file(s): 399
 2/3,K/1 (Item 1 from file: 162)  Links
   Fulltext available through:   USPTO Full Text Retrieval Options
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Global Health

0004672263 CAB Accession Number: 19982008802
Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM SUB 197 in United States infants.

Rennels, M. B.; Edwards, K. M.; Keyserling, H. L.; Reisinger, K. S.; Hogerman, D. A.; Madore, D. V.; Chang, I.; Paradiso, P. R.; Malinoski, F. J.; Kimura, A.
Center for Vaccine Development and Department of Pediatrics, University of Maryland School of Medicine, Baltimore, MD, USA.
Pediatrics vol. 101 (4): p.604-611
Publication Year: 1998
ISSN: 0031-4005
Language: English Record Type: Abstract
Document Type: Journal article
The safety and immunogenicity of heptavalent pneumococcal saccharide vaccine (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F) individually conjugated to CRM SUB 197...
...M.; Keyserling, H. L.; Reisinger, K. S.; Hogerman, D. A.; Madore, D. V.; Chang, I.; Paradiso, P. R.; Malinoski, F. J.; Kimura, A.

2/3,K/2 (Item 1 from file: 399) Links
CA SEARCH(R)

147392200 CA: 147(18)392200a PATENT
Multivalent pneumococcal polysaccharide-protein conjugate composition
Inventor (Author): Hausdorff, William P.; Siber, George Rainer; Paradiso, Peter R.; Prasad, A. Krishna
Location: USA
Assignee: Wyeth, John, and Brother Ltd.
Patent: U.S. Pat. Appl. Publ. ; US 20070231340 A1 Date: 20071004
Application: US 2006644924 (20061222) *US 2005PV669605 (20050408) *US 2006395593 (20060331)
Pages: 26pp., Cont.-in-part of U.S. Ser. No. 395,593.
CODEN: USXXCO
Language: English
Patent Classifications:
  Class: 424184100
   IPCR/8 + Level Value Position Status Version Action Source Office:
     A61K-0038/00 A I F B 20060101 20071004 H US
     C07K-0014/00 A I L B 20060101 20071004 H US

2/3,K/3 (Item 2 from file: 399) Links
  Fulltext available through: USPTO Full Text Retrieval Options
CA SEARCH(R)

147341890 CA: 147(16)341890t JOURNAL
Estimating the protective concentration of anti-pneumococcal capsular polysaccharide antibodies
Author: Siber, George R.; Chang, Ih; Baker, Sherryl; Fernsten, Philip; O'Brien, Katherine L.; Santosham, Mathuram; Klugman, Keith P.; Madhi, Shabir A.; Paradiso, Peter; Kohberger, Robert
Location: Wyeth Vaccines Research, Pearl River, NY, USA
Journal: Vaccine
Date: 2007
Volume: 25 Number: 19 Pages: 3816-3826
CODEN: VACCDE
ISSN: 0264-410X
Publisher Item Identifier: 0264-410X(07)00156-9
Language: English

Publisher: Elsevier Ltd.

2/3,K/4 (Item 3 from file: 399) Links
CA SEARCH(R)

147197430 CA: 147(9)197430y PATENT
Vaccines containing pneumococcal polysaccharide-protein conjugates and aluminum-based adjuvants
Inventor (Author): Hausdorff, William P.; Siber, George Rainer; Paradiso, Peter R.; Prasad, A. Krishna
Location: USA
Assignee: Wyeth, John, and Brother Ltd.
Patent: U.S. Pat. Appl. Publ. ; US 20070184071 A1 Date: 20070809
Application: US 2006644095 (20061222) *US 2005PV669605 (20050408) *US 2006395593 (20060331)
Pages: 26pp., Cont.-in-part of U.S. Ser. No. 395,593.
CODEN: USXXCO
Language: English
Patent Classifications:
Class: 424244100
IPCR/8 + Level Value Position Status Version Action Source Office:
A61K-0039/09 A I F B 20060101 20070809 H US
C07K-0014/31 A I L B 20060101 20070809 H US

2/3,K/5 (Item 4 from file: 399) Links
CA SEARCH(R)

147197429 CA: 147(9)197429e PATENT
Vaccines containing pneumococcal polysaccharide-protein conjugate and pH buffers
Inventor (Author): Hausdorff, William P.; Siber, George Rainer; Paradiso, Peter R.; Prasad, A. Krishna
Location: USA
Assignee: Wyeth, John, and Brother Ltd.
Patent: U.S. Pat. Appl. Publ. ; US 20070184072 A1 Date: 20070809
Application: US 2006644207 (20061222) *US 2005PV669605 (20050408) *US 2006395593 (20060331)
Pages: 26pp., Cont.-in-part of U.S. Ser. No. 395,593.
CODEN: USXXCO
Language: English
Patent Classifications:
Class: 424244100
IPCR/8 + Level Value Position Status Version Action Source Office:
A61K-0039/09 A I F B 20060101 20070809 H US
C07K-0014/31 A I L B 20060101 20070809 H US

2/3,K/6 (Item 5 from file: 399) Links
CA SEARCH(R)

145417019 CA: 145(21)417019x PATENT
Multivalent pneumococcal polysaccharide-protein conjugate vaccine
Inventor (Author): Hausdorff, William P.; Siber, George Rainer; Paradiso, Peter R.
Location: USA
Assignee: Wyeth, John, and Brother Ltd.
Patent: U.S. Pat. Appl. Publ. ; US 20060228380 A1 Date: 20061012
Application: US 2006395593 (20060331) *US 2005PV669605 (20050408)
Pages: 25pp.
CODEN: USXXCO

Language: English
Patent Classifications:
  Class: 424244100
   IPCR/8 + Level Value Position Status Version Action Source Office:
     A61K-0039/09   A I F B   20060101 20061012 H US

 2/3,K/7 (Item 1 from file: 315) Links
ChemEng & Biotec Abs
347574 CEABA Accession No.: 25-11-018887
 Document Type: Patent
Combination paediatric vaccine with enhanced immunogenicity of each vaccine component.

Author: Paradiso, P. R.; Hogerman, D. A.; Madore, D. V.; Hackel, J. G.
Corporate Source: American Cyanamid Co. Stamford, CT 06904-0060 USA
CODEN: EPXXDW
Patent Number: EP 594950
Publication Date: 4 May 1994 (940504)   Language: English
Priority Patent Application & Date: US 966995 (921027)
Author: Paradiso, P. R.; Hogerman, D. A.; Madore, D. V.; Hackel, J. G.
Abstract: ...mixture of diphtheria, tetanus, and pertussis antigens and a conjugate of fragments of the capsular polysaccharide antigen of Haemophilus influenzae type b and CRM197 protein.

 2/3,K/8 (Item 1 from file: 358) Links
Current BioTech Abs
066511 CBA Accession Number: 12-11-008190
Document Type: Patent
Combination paediatric vaccine with enhanced immunogenicity of each vaccine component.

Author: Paradiso, P. R.; Hogerman, D. A.; Madore, D. V.; Hackel, J. G.
Corporate Source: American Cyanamid Co. , Stamford, CT 06904-0060 , USA
CODEN: EPXXDW
Patent Number: EP 594950
Patent Application: US 966995 (921027)
Publication Date: 4 May 1994 (940504)   Language: English
Author: Paradiso, P. R.; Hogerman, D. A.; Madore, D. V.; Hackel, J. G.
Abstract: ...mixture of diphtheria, tetanus, and pertussis antigens and a conjugate of fragments of the capsular polysaccharide antigen of Haemophilus influenzae type b and CRM197 protein.

 2/3,K/9 (Item 1 from file: 149) Links
TGG Health&Wellness DB(SM)

01766556   Supplier Number: 20605969 (USE FORMAT 7 OR 9 FOR FULL TEXT)
Safety and immunogenicity of heptavalent pneumococcal vaccine conjugated to CRM197 in United States infants.

Rennels, MArgaret B.; Edwards, Kathryn M.; Keyserling, Harry L.; Reisinger, Keith S.; Hogerman, Deborah A.; Madore, Dace V.; Chang, Ih; Paradiso, Peter R.; Malinowski, Frank J.; Kimura, Alan
Pediatrics , v101 , n4 , p604(8)
April ,
1998
  Publication Format: Magazine/Journal
ISSN: 0031-4005
Language: English
Record Type: Abstract Target Audience: Professional
...Paradiso, Peter R

Author Abstract: Objective. To determine the safety and immunogenicity of heptavalent pneumococcal saccharide vaccine (serotypes 4, 6B, 9V, 14, 18C, 19F, 23F) individually conjugated to (CRM.sub.197...

```
?  d s
Set     Items   Description
S1         96   S E1-E7
S2          9   S S1 AND SACCHARIDE

?  e au=prasad, kr?
Ref   Items  Index-term
E1        2  AU=PRASAD, KP
E2        3  AU=PRASAD, KR
E3        0  AU=PRASAD, KR?
E4        2  AU=PRASAD, KRIS
E5       32  AU=PRASAD, KRISHNA
E6        1  AU=PRASAD, KRISHNA A.K.
E7        1  AU=PRASAD, KRISHNA A.V.
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E9        1  AU=PRASAD, KRISHNA B.S.
E10       1  AU=PRASAD, KRISHNA C
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E15       6  AU=PRASAD, KRISHNA K.
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E18       2  AU=PRASAD, KRISHNA KUMAR
E19       1  AU=PRASAD, KRISHNA M.
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E21       2  AU=PRASAD, KRISHNA R
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E23       1  AU=PRASAD, KRISHNA S.
E24       2  AU=PRASAD, KRISHNA V.
E25      24  AU=PRASAD, KRISHNAMACHAR
         Enter PAGE for more

?  s e1-e21
           2   AU=PRASAD, KP
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           2   AU=PRASAD, KRISHNA R
S3        69   S E1-E21
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             2   AU=PRASAD, KRISHNA V.
S4          73   S E1-E24

?  s s4 and saccharide
            73   S4
        197313   SACCHARIDE
S5           0   S S4 AND SACCHARIDE

?  s s4 and conjugate
            73   S4
        335861   CONJUGATE
S6           0   S S4 AND CONJUGATE

?  s s4 and multivalent
            73   S4
         30991   MULTIVALENT
S7           0   S S4 AND MULTIVALENT

?  d s
Set     Items   Description
S1         96   S E1-E7
S2          9   S S1 AND SACCHARIDE
S3         69   S E1-E21
S4         73   S E1-E24
S5          0   S S4 AND SACCHARIDE
S6          0   S S4 AND CONJUGATE
S7          0   S S4 AND MULTIVALENT


?  s Streptococcus pneumoniae or S. pneumoniae or Pneumococcal
         72494   STREPTOCOCCUS PNEUMONIAE
           210   S. PNEUMONIAE
         71403   PNEUMOCOCCAL
S1      116432   S STREPTOCOCCUS PNEUMONIAE OR S. PNEUMONIAE OR PNEUMOCOCCAL

?  s conjugate and vaccine
        287735   CONJUGATE
        715472   VACCINE
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```
S2      23314   S CONJUGATE AND VACCINE

?
?  s multivalent conjugate
S3          0   S MULTIVALENT CONJUGATE

?
?  s multivalent
S4      27619   S MULTIVALENT

?  s capsular polysaccharide
S5       2369   S CAPSULAR POLYSACCHARIDE

?
?  s Immunogenic
S6      96943   S IMMUNOGENIC

?
?  s 13vPNC
S7          0   S 13VPNC

?  s glycoconjugate vaccine
S8         40   S GLYCOCONJUGATE VACCINE

?
?  s 23-Valent Pneumococcal Conjugate Vaccine
S9          1   S 23-VALENT PNEUMOCOCCAL CONJUGATE VACCINE

?
?  s 13-Valent Pneumococcal Conjugate Vaccine
S10         0   S 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE

?
?  s 9-Valent Pneumococcal Conjugate Vaccine
S11         8   S 9-VALENT PNEUMOCOCCAL CONJUGATE VACCINE

?
?  s 13 polysaccharide protein conjugate
S12         0   S 13 POLYSACCHARIDE PROTEIN CONJUGATE

?  s sertoype? and (1 and 4 and 5 and 6A and 6B and 7F and 9V and 14 and 18C and 19A
and 19F and 23F)
           13   SERTOYPE?
     38091063   1
     25426828   4
     24326987   5
       122539   6A
        47519   6B
         5359   7F
         3798   9V
      4912159   14
         3488   18C
         5072   19A
        16653   19F
         4229   23F
S13         0   S SERTOYPE? AND (1 AND 4 AND 5 AND 6A AND 6B AND 7F AND 9V AND 14
AND 18C AND 19A AND 19F AND 23F)

?  s serotype 3
S14       137   S SEROTYPE 3

?  s serotype 1
S15       234   S SEROTYPE 1
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? s serotype 4
S16        96   S SEROTYPE 4

? s SEROTYPE 5
S17       116   S SEROTYPE 5

? s SEROTYPE 6A
S18        15   S SEROTYPE 6A

? s SEROTYPE 6B
S19        44   S SEROTYPE 6B

? s SEROTYPE 7F
S20         9   S SEROTYPE 7F

? s SEROTYPE 9V
S21        18   S SEROTYPE 9V

? s serotype 14
S22        60   S SEROTYPE 14

? s serptype 18C
S23         0   S SERPTYPE 18C

? s serotype 19A
S24        11   S SEROTYPE 19A

? s serotype 19F
S25        33   S SEROTYPE 19F

? s serotype 23F
S26        35   S SEROTYPE 23F

? s s15 and s14 and s17 and s18 and s20 and s24
          234   S15
          137   S14
          116   S17
           15   S18
            9   S20
           11   S24
S27         0   S S15 AND S14 AND S17 AND S18 AND S20 AND S24

? d s
Set     Items   Description
S1     116432   S STREPTOCOCCUS PNEUMONIAE OR S. PNEUMONIAE OR PNEUMOCOCCAL
S2      23314   S CONJUGATE AND VACCINE
S3          0   S MULTIVALENT CONJUGATE
S4      27619   S MULTIVALENT
S5       2369   S CAPSULAR POLYSACCHARIDE
S6      96943   S IMMUNOGENIC
S7          0   S 13VPNC
S8         40   S GLYCOCONJUGATE VACCINE
S9          1   S 23-VALENT PNEUMOCOCCAL CONJUGATE VACCINE
S10         0   S 13-VALENT PNEUMOCOCCAL CONJUGATE VACCINE
S11         8   S 9-VALENT PNEUMOCOCCAL CONJUGATE VACCINE
S12         0   S 13 POLYSACCHARIDE PROTEIN CONJUGATE
S13         0   S SERTOYPE? AND (1 AND 4 AND 5 AND 6A AND 6B AND 7F AND 9V AND 14
AND 18C AND 19A AND 19F AND 23F)
S14       137   S SEROTYPE 3
S15       234   S SEROTYPE 1
S16        96   S SEROTYPE 4
S17       116   S SEROTYPE 5
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S18         15   S SEROTYPE 6A
S19         44   S SEROTYPE 6B
S20          9   S SEROTYPE 7F
S21         18   S SEROTYPE 9V
S22         60   S SEROTYPE 14
S23          0   S SERPTYPE 18C
S24         11   S SEROTYPE 19A
S25         33   S SEROTYPE 19F
S26         35   S SEROTYPE 23F
S27          0   S S15 AND S14 AND S17 AND S18 AND S20 AND S24

?  s s1 and s4
       116432   S1
        27619   S4
S28       314   S S1 AND S4

?  s s28 and conjugate
          314   S28
       287735   CONJUGATE
S29       176   S S28 AND CONJUGATE

?  s s29 and serotype 3
          176   S29
          137   SEROTYPE 3
S30         0   S S29 AND SEROTYPE 3

?  s s29 and s6
          176   S29
        96943   S6
S31        41   S S29 AND S6

?  rd
>>>W:  Duplicate detection is not supported for File 393.
Duplicate detection is not supported for File 391.
Records from unsupported files will be retained in the RD set.
S32         13   RD  (UNIQUE ITEMS)

?  s s32 and s8
           13   S32
           40   S8
S33         0   S S32 AND S8

?  s s32 and glycoconjugate
           13   S32
        18096   GLYCOCONJUGATE
S34         0   S S32 AND GLYCOCONJUGATE

?  t s32/free/1-13
>>>W:  "FREE" is not a valid format name in file(s): 399
 32/6/1 (Item 1 from file: 5)  Links

0016041579   Biosis No.: 200600386974
A review of vaccine research and development: Meningococcal disease

2006


 32/6/2 (Item 2 from file: 5)  Links

0012922199   Biosis No.: 200100094038
Serotype of Streptococcus pneumoniae capsular polysaccharide can modify the Th1/Th2
cytokine profile and IgG subclass response to pneumococal-CRM197 conjugate vaccines
in a murine model
```

2000

32/6/3 (Item 3 from file: 5) Links

0012756043 Biosis No.: 200000474356
Immunogenicity and reactogenicity of a pneumococcal conjugate vaccine administered combined with a Haemophilus influenzae type b conjugate vaccine in United Kingdom infants

2000

32/6/4 (Item 4 from file: 5) Links

0012515359 Biosis No.: 200000233672
Immunogenicity of pneumococcal conjugate vaccines

2000

32/6/5 (Item 5 from file: 5) Links

0012479786 Biosis No.: 200000198099
Preparation of pneumococcal capsular polysaccharide-protein conjugate vaccines utilizing new fragmentation and conjugation technologies

2000

32/6/6 (Item 1 from file: 24) Links
CSA Life Sciences Abstracts

0002173337 IP Accession No: 4820047
Serotype of Streptococcus pneumoniae capsular polysaccharide can modify the Th1/Th2 cytokine profile and IgG subclass response to pneumococal-CRM sub(197) conjugate vaccines in a murine model

Publication Date: 2000

Descriptors: Vaccines; Immunoglobulin G; Capsules; Lymphocytes T; Helper cells; Streptococcus pneumoniae; polysaccharides; Streptococcus pneumoniae
Identifiers: immunology; mice
Subj Catg: 06807, Active immunization; 02834, Vaccination and immunization

32/6/7 (Item 2 from file: 24) Links
CSA Life Sciences Abstracts

0001811025 IP Accession No: 4264490
PspA and PspC: Their potential for use as Pneumococcal vaccines

Publication Date: 1997

Descriptors: vaccines; PspA protein; PspC protein; immunogenicity; Streptococcus pneumoniae
Subj Catg: 02834, Vaccination and immunization; 01099, Bacteria and fungi

32/6/8 (Item 1 from file: 34) Links
SciSearch(R) Cited Ref Sci

12559626 Genuine Article#: 800AK Number of References: 36
Immune response of healthy women to 2 different group B streptococcal type V capsular polysaccharide-protein conjugate vaccines
(ABSTRACT AVAILABLE)
Publication date: 20040315
Journal Subject Category: INFECTIOUS DISEASES
Identifiers-- KeyWord Plus(R): SEROTYPE-V; PNEUMOCOCCAL POLYSACCHARIDE; STRUCTURAL DETERMINATION; ANTIBIOTIC-PROPHYLAXIS; IMMUNOGENICITY; ANTIBODY; DISEASE; IA; IB; RECOMMENDATIONS

32/6/9 (Item 1 from file: 45) Links

01621146 EMCare No: 40269235
Capsular polysaccharide-protein conjugate vaccines targeting Streptococcus pneumoniae

ROLE DE LA VACCINATION SUR LES INFECTIONS INVASIVES A PNEUMOCOQUE
2005

32/6/10 (Item 1 from file: 144) Links
Pascal

14957251 PASCAL No.: 01-0109755

Serotype of Streptococcus pneumoniae capsular polysaccharide can modify the Th1/Th2 cytokine profile and IgG subclass response to pneumococal-CRM SUB 1 SUB 9 SUB 7 conjugate vaccines in a murine model

2000

English Descriptors: Mouse; Streptococcus pneumoniae; Vaccine; Conjugated compound; Carrier protein; Toxoid; Microorganism capsule; Polysaccharide; Serotype specificity; Immunogenicity; Humoral immunity; IgG; Isotype; T-Lymphocyte; Helper cell; Cell subpopulation; Cytokine
Broad Descriptors: Rodentia; Mammalia; Vertebrata; Streptococcaceae; Micrococcales; Bacteria; Rodentia; Mammalia; Vertebrata; Streptococcaceae ; Micrococcales; Bacterie; Rodentia; Mammalia; Vertebrata; Streptococcaceae; Micrococcales; Bacteria

French Descriptors: Souris; Streptococcus pneumoniae; Vaccin; Compose conjugue; Proteine transport; Anatoxine; Capsule microorganisme; Polyoside; Specificite serotype; Immunogenicite; Immunite humorale; IgG; Isotype; Lymphocyte T; Cellule helper; Sous population cellulaire; Cytokine

Classification Codes: 002A05B12

32/6/11 (Item 2 from file: 144) Links
Pascal

14596221 PASCAL No.: 00-0264290

Immunogenicity of pneumococcal conjugate vaccines : Treatment of Pediatric Infectious Diseases : Role of Pneumococcal

Conjugate Vaccines

2000

English Descriptors: Pneumococcal infection; Streptococcus pneumoniae; Prevention; Polyvalent vaccine; Immunogenicity; Serology; Immunological investigation; Infant; Child
Broad Descriptors: Streptococcal infection; Bacteriosis; Infection; Streptococcaceae; Micrococcales; Bacteria; Human; Streptococcie; Bacteriose; Infection; Streptococcaceae; Micrococcales; Bacterie; Homme; Estreptococia; Bacteriosis; Infeccion; Streptococcaceae; Micrococcales; Bacteria; Hombre

French Descriptors: Pneumococcie; Streptococcus pneumoniae; Prevention; Vaccin polyvalent; Immunogenicite; Serologie; Exploration immunologique; Nourrisson; Enfant

Classification Codes: 002B05A02

32/6/12 (Item 1 from file: 135) Links
NewsRx Weekly Reports

0000043582 (USE FORMAT 7 OR 9 FOR FULLTEXT)

Conjugate Vaccines Immunogenic in Young Children

Word Count:
311

June 6, 2000 (20000606)

DESCRIPTORS: bacteriology; cell biology; drug resistance; epidemiology; immunoglobulins; immunology; therapeutic; therapies; therapy; vaccinology; communicable disease; public health; world disease
SUBJECT HEADING: Pneumococcal Vaccines

32/6/13 (Item 1 from file: 357) Links

0413666 DBA Accession No.: 2006-27162
Preparing a multivalent immunogenic composition comprises preparing a hepatitis B virus (HBV) component by purifying hepatitis B surface antigen (HBsAg), preparing a non-HBV component, and mixing the HBV and non-HBV components involving vector plasmid-mediated glyceraldehyde-3-phosphate-dehydrogenase and hepatitis B virus surface antigen gene transfer and expression in Saccharomyces cerevisiae for use in therapy 2006